

=> fil reg

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STRUCTURE FILE UPDATES: 11 OCT 2004 HIGHEST RN 760932-70-5  
DICTIONARY FILE UPDATES: 11 OCT 2004 HIGHEST RN 760932-70-5

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

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to the file summary sheet on the web at:  
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> d que 16

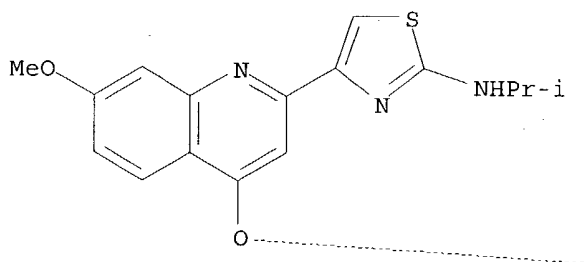
L6 1 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/RN

=> d ide

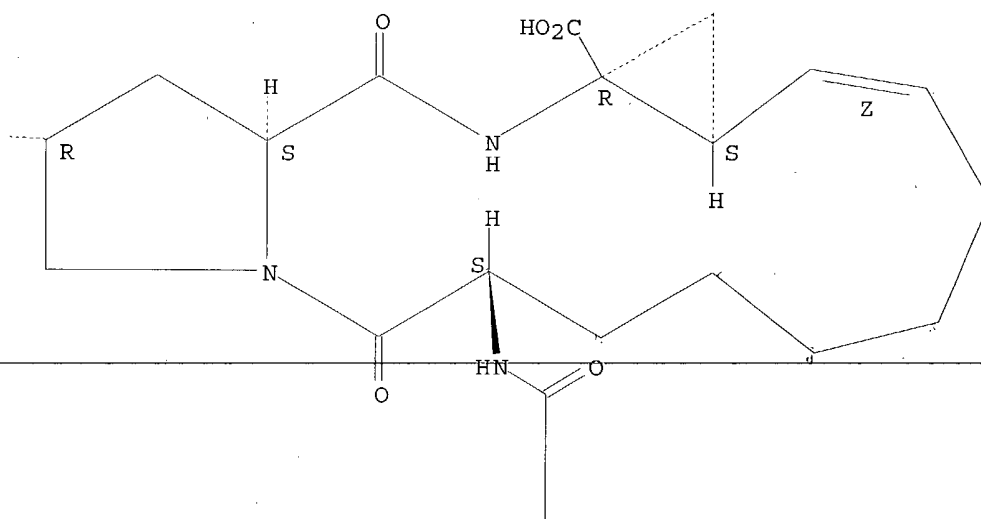
L6 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN  
RN 300832-84-2 REGISTRY  
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic  
acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16  
,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-  
4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA  
INDEX NAME)  
OTHER NAMES:  
CN BILN 2061  
CN BILN 2061ZW  
CN Ciluprevir  
FS STEREOSEARCH  
MF C40 H50 N6 O8 S  
SR CA  
LC STN Files: ADISINSIGHT, CA, CAPLUS, IMSRESEARCH, PHAR, PROUSDDR,  
TOXCENTER, USPATFULL  
DT.CA CAPLUS document type: Journal; Patent  
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC  
(Process); RACT (Reactant or reagent); USES (Uses)  
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation);  
PRP (Properties); USES (Uses)

Absolute stereochemistry.  
Double bond geometry as shown.

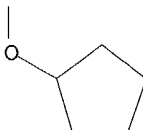
PAGE 1-A



PAGE 1-B



PAGE 2-B



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

15 REFERENCES IN FILE CA (1907 TO DATE)  
15 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> FIL STNGUIDE

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=> => fil reg

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STRUCTURE FILE UPDATES: 11 OCT 2004 HIGHEST RN 760932-70-5  
DICTIONARY FILE UPDATES: 11 OCT 2004 HIGHEST RN 760932-70-5

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=> fil hcap

FILE 'HCAPLUS' ENTERED AT 12:19:27 ON 13 OCT 2004  
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FILE COVERS 1907 - 13 Oct 2004 VOL 141 ISS 16  
FILE LAST UPDATED: 12 Oct 2004 (20041012/ED)

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

=> fil medlin

FILE 'MEDLINE' ENTERED AT 12:19:32 ON 13 OCT 2004

FILE LAST UPDATED: 12 OCT 2004 (20041012/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLD MEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nlm.nih.gov/pubs/techbull/nd03/nd03\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html) for a description of changes.

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=> fil embase

FILE 'EMBASE' ENTERED AT 12:19:35 ON 13 OCT 2004

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FILE COVERS 1974 TO 7 Oct 2004 (20041007/ED)

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=> fil biosis

FILE 'BIOSIS' ENTERED AT 12:19:38 ON 13 OCT 2004

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FILE COVERS 1969 TO DATE.

~~CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNS) PRESENT~~  
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 6 October 2004 (20041006/ED)

FILE RELOADED: 19 October 2003.

=> fil adisinsight

FILE 'ADISINSIGHT' ENTERED AT 12:19:47 ON 13 OCT 2004

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FILE COVERS 1986 TO 7 Oct 2004 (20041007/ED)

FILE LAST UPDATED: 7 OCT 2004 (20041007/ED)

=> fil imsresearch

FILE 'IMSRESEARCH' ENTERED AT 12:19:53 ON 13 OCT 2004

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FILE COVERS 1977 TO 8 Oct 2004 (20041008/ED)

#####  
#

```
#          !!! ATTENTION !!!          #
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# at +44(0)20-7393-5888, or email globaldirect@uk.imshealth.com #
# See HELP SUBSCRIPTION for more information. #
#                                     #
#####
```

This file contains CAS Registry Numbers for easy and accurate substance identification.

The file name was changed from DRUGUPDATES to IMSRESEARCH on 7 Dec. 2003.  
The file name DRUGUPDATES is now an alias for IMSRESEARCH.

=> fil phar

FILE 'PHAR' ENTERED AT 12:20:00 ON 13 OCT 2004  
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FILE RELOADED May 4, 2003  
FILE LAST UPDATED: Oct 8, 2004 (20041008/ED)

PHAR was reloaded and enhanced with pharmacokinetic information and systematic chemical names. Enter HELP RLOAD at an arrow prompt in PHAR for the reload information.

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FILE COVERS 1907 TO 5 Oct 2004 (20041005/ED)

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TOXCENTER has been enhanced with new files segments and search fields.  
See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nlm.nih.gov/pubs/techbull/nd03/nd03\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html) for a description of changes.

=> fil uspatfull

FILE 'USPATFULL' ENTERED AT 12:20:12 ON 13 OCT 2004  
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 12 Oct 2004 (20041012/PD)  
FILE LAST UPDATED: 12 Oct 2004 (20041012/ED)  
HIGHEST GRANTED PATENT NUMBER: US6804828  
HIGHEST APPLICATION PUBLICATION NUMBER: US2004199971  
CA INDEXING IS CURRENT THROUGH 12 Oct 2004 (20041012/UPCA)  
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 12 Oct 2004 (20041012/PD)  
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2004  
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2004

>>> USPAT2 is now available. USPATFULL contains full text of the <<<  
>>> original, i.e., the earliest published granted patents or <<<  
>>> applications. USPAT2 contains full text of the latest US <<<  
>>> publications, starting in 2001, for the inventions covered in <<<  
>>> USPATFULL. A USPATFULL record contains not only the original <<<  
>>> published document but also a list of any subsequent <<<  
>>> publications. The publication number, patent kind code, and <<<  
>>> publication date for all the US publications for an invention <<<  
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<  
>>> records and may be searched in standard search fields, e.g., /PN, <<<  
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<  
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<  
>>> enter this cluster. <<<  
>>> <<<

---

>>> Use USPATALL when searching terms such as patent assignees, <<<  
>>> classifications, or claims, that may potentially change from <<<  
>>> the earliest to the latest publication. <<<

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=> fil wpix

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FILE LAST UPDATED: 11 OCT 2004 <20041011/UP>  
MOST RECENT DERWENT UPDATE: 200465 <200465/DW>  
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,  
PLEASE VISIT:  
[http://www.stn-international.de/training\\_center/patents/stn\\_guide.pdf](http://www.stn-international.de/training_center/patents/stn_guide.pdf) <<<

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=> file stnguide

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LAST RELOADED: Oct 8, 2004 (20041008/UP).

=> d que 115

L6 1 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/RN  
L7 0 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/CRN  
L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON (L6 OR L7)  
L9 15 SEA FILE=HCAPLUS ABB=ON PLU=ON L8  
L10 0 SEA FILE=HCAPLUS ABB=ON PLU=ON 300832-84-2D?  
L11 15 SEA FILE=HCAPLUS ABB=ON PLU=ON L9 OR L10  
L12 SEL PLU=ON L8 1- CHEM : 4 TERMS  
L13 17 SEA FILE=HCAPLUS ABB=ON PLU=ON L12  
L14 6 SEA FILE=HCAPLUS ABB=ON PLU=ON 300832-84-2P  
L15 17 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10 OR L11) OR (L13 OR  
L14)

=>

(FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 12:01:12 ON 13 OCT 2004)

=> d que 126

L6 1 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/RN  
L7 0 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/CRN  
L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON (L6 OR L7)  
L16 SEL PLU=ON L8 1- CHEM : 4 TERMS  
L17 74 SEA L16  
L18 345253 SEA ?CRYST?  
L19 1408058 SEA ?PHASE? OR ?PHASIC?  
L20 2861999 SEA ?MORPH?  
L21 1578978 SEA FORM  
L22 8 SEA L17 (L) (L18 OR L19 OR L20 OR L21)  
L23 4478959 SEA ?STRUCTUR?  
L24 11 SEA L17 (L) L23  
L25 16 SEA L22 OR L24  
L26 8 DUP REM L25 (8 DUPLICATES REMOVED)

L20 —  
picked up  
"morphine"

=>

(FILE 'ADISINSIGHT, IMSRESEARCH, PHAR, TOXCENTER' ENTERED AT 12:07:26 ON  
13 OCT 2004)

=> d que 129

L6 1 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/RN  
L7 0 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/CRN  
L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON (L6 OR L7)  
L27 SEL PLU=ON L8 1- CHEM : 4 TERMS  
L28 12 SEA L27  
L29 12 DUP REM L28 (0 DUPLICATES REMOVED)

=> d que 131

L6 1 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/RN  
L7 0 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/CRN  
L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON (L6 OR L7)  
L30 SEL PLU=ON L8 1- CHEM : 4 TERMS  
L31 6 SEA FILE=USPATFULL ABB=ON PLU=ON L30

=> d que 140

L35 2 SEA FILE=WPIX ABB=ON PLU=ON (BILN-2061/BIX OR CILUPREVIR/BIX)  
  
L36 2 SEA FILE=WPIX ABB=ON PLU=ON (BILN(1W)2061 OR ?CILUPREV IR OR  
?CILU PREVIR? OR CI LUPREVIR?)/BIX  
L37 2 SEA FILE=WPIX ABB=ON PLU=ON (L35 OR L36)  
L38 0 SEA FILE=WPIX ABB=ON PLU=ON L37 AND ?CRYST?  
L39 0 SEA FILE=WPIX ABB=ON PLU=ON L37 AND ?CRYST?/BIX  
L40 2 SEA FILE=WPIX ABB=ON PLU=ON (L37 OR L38 OR L39)

=> dup rem 115 126 129 131 140

DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, IMSRESEARCH, PHAR'.  
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE

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PROCESSING COMPLETED FOR L26  
PROCESSING COMPLETED FOR L29  
PROCESSING COMPLETED FOR L31  
PROCESSING COMPLETED FOR L40

L41 36 DUP REM L15 L26 L29 L31 L40 (9 DUPLICATES REMOVED)  
ANSWERS '1-17' FROM FILE HCAPLUS  
ANSWERS '18-19' FROM FILE MEDLINE  
ANSWERS '20-22' FROM FILE BIOSIS  
ANSWERS '23-25' FROM FILE ADISINSIGHT  
ANSWERS '26-27' FROM FILE IMSRESEARCH  
ANSWERS '28-29' FROM FILE PHAR  
ANSWERS '30-31' FROM FILE TOXCENTER  
ANSWERS '32-36' FROM FILE USPATFULL

=> d iall retable

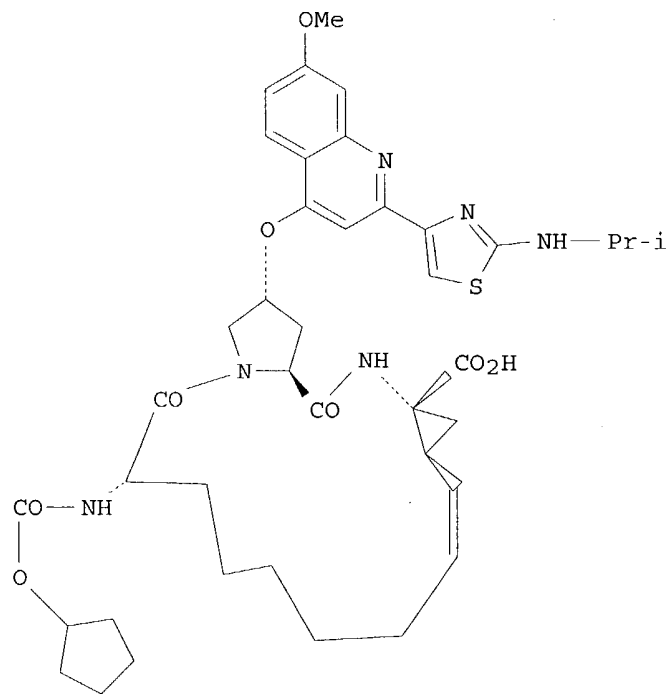
L41 ANSWER 1 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE.1  
ACCESSION NUMBER: 2004:310970 HCAPLUS  
DOCUMENT NUMBER: 140:327091  
ENTRY DATE: Entered STN: 16 Apr 2004  
TITLE: Potent inhibitor of HCV serine protease  
INVENTOR(S): Chen, Shirlynn; Nehmiz, Gerhard; Croenlein, Jens  
Oliver; Steinmann, Gerhard; Gunn, Jocelyn Abella;  
Costa, Phuong Do  
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany  
SOURCE: PCT Int. Appl., 42 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
INT. PATENT CLASSIF.:  
MAIN: A61K031-4709  
SECONDARY: A61K045-06; A61P031-14  
CLASSIFICATION: 63-6 (Pharmaceuticals)  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004030670	A1	20040415	WO 2003-US30402	20030925
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2004138109	A1	20040715	US 2003-663220	20030916
PRIORITY APPLN. INFO.:			US 2002-414940P	P 20020930
			US 2002-421904P	P 20021029
			US 2002-433834P	P 20021216
			US 2003-443662P	P 20030130

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004030670	ICM	A61K031-4709
	ICS	A61K045-06; A61P031-14

GRAPHIC IMAGE:



I

## ABSTRACT:

Disclosed are oral pharmaceutical compns., kits and methods of treating and preventing Hepatitis C Viral (HCV) infections wherein Compound (I), a potent inhibitor of HCV serine protease, or a pharmaceutically acceptable salt thereof, is administered in a selected dosage range. Also disclosed are the use of I or a pharmaceutically acceptable salt thereof, as a control substance for validating an HCV replication assay and also as a control substance for determining the relative effectiveness of one or more substances, alone or in combination, to inhibit the replication of HCV.

SUPPL. TERM: HCV serine proteinase inhibitor  
 INDEX TERM: Drug delivery systems  
 (carriers; potent inhibitor of HCV serine protease)  
 INDEX TERM: Cytoprotective agents  
 (hepatoprotective; potent inhibitor of HCV serine protease)  
 INDEX TERM: Hepatitis A virus  
 Hepatitis B virus  
 Human immunodeficiency virus  
 (inhibitors; potent inhibitor of HCV serine protease)  
 INDEX TERM: Antiviral agents  
 Hepatitis C virus  
 Human  
 Immunomodulators  
 Solvents  
 (potent inhibitor of HCV serine protease)  
 INDEX TERM: Polyoxyalkylenes, biological studies

ROLE: NUU (Other use, unclassified); THU (Therapeutic use);  
 BIOL (Biological study); USES (Uses)  
 (solvent; potent inhibitor of HCV serine protease)

INDEX TERM: 37259-58-8, Serine proteinase  
 ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
 (HCV, inhibitors; potent inhibitor of HCV serine protease)

INDEX TERM: 300832-84-2  
 ROLE: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
 (potent inhibitor of HCV serine protease)

INDEX TERM: 57-55-6, Propylene glycol, biological studies 64-17-5, Ethanol, biological studies 7732-18-5, Water, biological studies 25322-68-3, Polyethylene glycol  
 ROLE: NUU (Other use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (solvent; potent inhibitor of HCV serine protease)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S): (1) Anon; CURRENT DRUG DISCOVERY 2002, P45  
 (2) Boehringer Ingelheim Ca Ltd; WO 0059929 A 2000 HCAPLUS  
 (3) Boehringer Ingelheim Pharma; WO 03066103 A 2003 HCAPLUS

## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	2002		45	CURRENT DRUG DISCOVE	
Boehringer Ingelheim Ca	2000			WO 0059929 A	HCAPLUS
Boehringer Ingelheim Ph	2003			WO 03066103 A	HCAPLUS

=&gt; d iall retable 2-17

L41 ANSWER 2 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2004:142968 HCAPLUS

DOCUMENT NUMBER: 140:193056

ENTRY DATE: Entered STN: 22 Feb 2004

TITLE: Combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compositions, and use in the treatment of cytokine-mediated diseases

INVENTOR(S): Simianer, Stefan; Bilbault, Pascal; Cappola, Michael L.; Way, Susan Lynn

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA; Boehringer Ingelheim France

SOURCE: PCT Int. Appl., 168 pp.  
 CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

INT. PATENT CLASSIF.:  
 MAIN: A61K031-5377  
 SECONDARY: A61K031-505; A61K031-42; A61K039-395; A61K031-427; A61K031-506; A61P001-00; A61P017-06; A61P019-02

CLASSIFICATION: 1-7 (Pharmacology)  
 Section cross-reference(s): 28, 63

FAMILY ACC. NUM. COUNT: 1

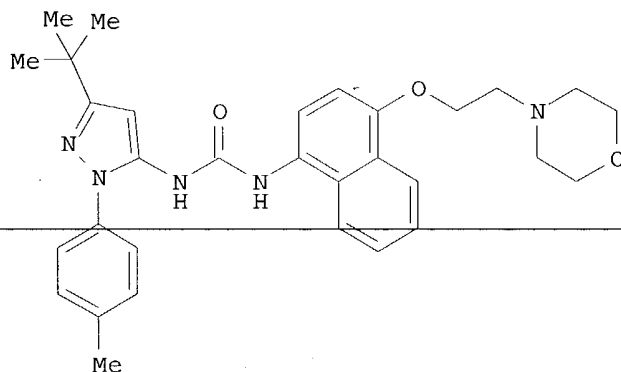
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014387	A1	20040219	WO 2003-US25341	20030812
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004110755	A1	20040610	US 2003-638702	20030811
PRIORITY APPLN. INFO.:			US 2002-403115P	P 20020813

## PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004014387	ICM	A61K031-5377
	ICS	A61K031-505; A61K031-42; A61K039-395; A61K031-427; A61K031-506; A61P001-00; A61P017-06; A61P019-02

GRAPHIC IMAGE:



## ABSTRACT:

The invention relates to pharmaceutical combination therapies based on p38 kinase inhibitors and another active ingredients, pharmaceutical compns. comprising such combinations, processes for preparing them, and their use in the treatment of cytokine-mediated diseases. Preparation of I (BIRB 796 BS) is described.

SUPPL. TERM: cytokine disease therapeutic p38 MAP kinase inhibitor combination; BIRB 796 BS prepn p38 MAP kinase inhibitor

INDEX TERM: Fusion proteins (chimeric proteins)

ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(CTLA4-Ig; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Intestine, disease

(Crohn's; combinations of active agents with p38 MAP

kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Selectins  
 ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
 (E-, inhibitors; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Cell adhesion molecules  
 ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
 (ICAM-1 (intercellular adhesion mol. 1), inhibitors; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Interleukin 1 receptors  
 ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
 (antagonists; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: CD4 (antigen)  
 ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
 (anti-CD4; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: CD80 (antigen)  
 ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
 (anti-CD80; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Antibodies and Immunoglobulins  
 ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (anti-LFA3-IgC1; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Drugs  
 (biol. agents; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Angiogenesis inhibitors  
 Antirheumatic agents  
 Antiviral agents  
 Cytotoxic agents  
 Drug delivery systems  
 Human  
 Immunomodulators  
 Immunosuppressants  
 Photodynamic therapy  
 Phototherapy  
 Psoriasis  
 Rheumatoid arthritis  
 UV A radiation  
 UV B radiation  
 (combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: CTLA-4 (antigen)  
Cytokines  
Interleukin 10  
Interleukin 6  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Antibodies and Immunoglobulins  
Glucocorticoids  
Macrolides  
Retinoids  
Steroids, biological studies  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Fusion proteins (chimeric proteins)  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(diphtheria toxin fragment DAB389; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Fusion proteins (chimeric proteins)  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(diphtheria toxin; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Toxins  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(diphtheria, DAB389, fusion products; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Toxins  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
(diphtheria, DAB389; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Toxins  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(diphtheria, fusion products; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Interleukin 2  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(fusion products; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Antibodies and Immunoglobulins  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use);

BIOL (Biological study); USES (Uses)  
(fusion protein with CTLA-4; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: CTLA-4 (antigen)  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use);  
BIOL (Biological study); USES (Uses)  
(fusion protein with Ig; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Drugs  
(gastrointestinal; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Cell adhesion molecules  
LFA-1 (antigen)  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
(inhibitors; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Anti-inflammatory agents  
(nonsteroidal; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Drug delivery systems  
(tablets; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Interleukin 2 receptors  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
( $\alpha$  chain, anti-CD25; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Interferons  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use);  
BIOL (Biological study); USES (Uses)  
( $\alpha$ ; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Interferons  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use);  
BIOL (Biological study); USES (Uses)  
( $\beta$ ,  $\beta$ 1B; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 7631-86-9, Silicon Dioxide, biological studies  
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(Colloidal; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 9004-34-6, Cellulose, biological studies  
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(Microcryst.; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 9005-25-8, Starch, biological studies  
 ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (Pregelatinized; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 127464-60-2, Vascular endothelial growth factor  
 ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
 (agents against; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 80295-53-0, Complement c5 106362-32-7, Peptide T  
 165245-96-5, p38 Kinase  
 ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
 (combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 285983-48-4P, BIRB 796BS  
 ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 50-02-2, Dexamethasone 50-18-0, Cyclophosphamide  
 50-24-8, Prednisolone 50-35-1, Thalidomide 50-44-2, Mercaptopurine 50-78-2, Aspirin 52-67-5, D-Penicillamine 53-86-1, Indomethacin 54-21-7, Sodium salicylate 59-05-2, Methotrexate 61-68-7, Mefenamic acid 67-97-0D, Vitamin D3, analogs 80-08-0, Dapsone 83-43-2, Methylprednisolone 89-57-6, 5-ASA 103-90-2, Acetaminophen 118-42-3, Hydroxychloroquine 305-03-3, Chlorambucil 378-44-9, Betamethasone 446-86-6, Azathioprine 552-94-3, Salsalate 599-79-1, Sulfasalazine 1406-16-2, Vitamin D 2016-36-6, Choline salicylate, biological studies 3615-24-5, Ramifenazone 5104-49-4, Flurbiprofen 6385-02-0, Meclofenamate sodium 6493-05-6 10118-90-8, Minocycline 12244-57-4, Gold sodium thiomalate 14484-47-0, Deflazacort 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 18917-89-0, Magnesium salicylate 21256-18-8, Oxaprozin 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22494-42-4, Diflunisal 23187-87-3, Choline magnesiumsalicylate 26171-23-3, Tolmetin 31842-01-0, Indoprofen 33005-95-7, Tiaprofenic acid 33069-62-4, Taxol 34031-32-8, Auranofin 34597-40-5, Fenoprofen calcium 36322-90-4, Piroxicam 38194-50-2, Sulindac 41340-25-4, Etodolac 42924-53-8, Nabumetone 51333-22-3, Budesonide 51803-78-2, Nimesulide 53123-88-9, Sirolimus 53716-49-7, Carprofen 59865-13-3, Cyclosporine 70374-39-9, Lornoxicam 71125-38-7, Meloxicam 74103-07-4, Ketorolac tromethamine 75706-12-6, Leflunomide 80937-31-1, Flosulide 104987-11-3, Tacrolimus 104987-12-4, Ascomycin 128794-94-5, Mycophenolate mofetil 137071-32-0, Pimecrolimus 152923-56-3, Daclizumab 156679-34-4, Ro 45-2081 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 170277-31-3, Infliximab 179045-86-4, Basiliximab 181695-72-7, Valdecocix 185243-69-0, Etanercept 189261-10-7, Antegren

202409-33-4, Etoricoxib 214745-43-4, Efalizumab  
 222535-22-0, Alefacept 294848-51-4 294848-58-1  
 294849-20-0 294849-84-6 294850-04-7 294850-87-6  
 294851-64-2 **300832-84-2** 321656-57-9  
 331257-52-4, ISIS 2302 331731-18-1, Adalimumab  
 336128-48-4, CDP 571 662151-94-2, ISIS 8  
 ROLE: PAC (Pharmacological activity); THU (Therapeutic use);  
 BIOL (Biological study); USES (Uses)

(combinations of active agents with p38 MAP kinase  
 inhibitors, pharmaceutical compns., and use in treatment  
 of cytokine-mediated diseases)

INDEX TERM: 605-62-9, 4-Nitro-1-hydroxynaphthalene 637-60-5,  
 p-Tolylhydrazine hydrochloride 3647-69-6,  
 4-(2-Chloroethyl)morpholine hydrochloride 17341-93-4,  
 2,2,2-Trichloroethyl chloroformate 59997-51-2,  
 Pivaloylacetonitrile 317806-90-9

ROLE: RCT (Reactant); RACT (Reactant or reagent)  
 (combinations of active agents with p38 MAP kinase  
 inhibitors, pharmaceutical compns., and use in treatment  
 of cytokine-mediated diseases)

INDEX TERM: 317806-86-3P 317806-87-4P 317806-88-5P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP  
 (Preparation); RACT (Reactant or reagent)  
 (combinations of active agents with p38 MAP kinase  
 inhibitors, pharmaceutical compns., and use in treatment  
 of cytokine-mediated diseases)

INDEX TERM: 317806-89-6P

ROLE: SPN (Synthetic preparation); PREP (Preparation)  
 (combinations of active agents with p38 MAP kinase  
 inhibitors, pharmaceutical compns., and use in treatment  
 of cytokine-mediated diseases)

INDEX TERM: 66-97-7D, Psoralen, derivs. 557-04-0, Magnesium Stearate  
 9003-39-8, Povidone K30 9063-38-1, Sodium StarchGlycolate  
 64044-51-5, Lactose Monohydrate

ROLE: THU (Therapeutic use); BIOL (Biological study); USES  
 (Uses)  
 (combinations of active agents with p38 MAP kinase  
 inhibitors, pharmaceutical compns., and use in treatment  
 of cytokine-mediated diseases)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD.

- REFERENCE(S): (1) Anon; ARTHRITIS AND RHEUMATISM 2002, V46(2), P328  
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 PS175  
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 PS184  
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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	2002	46	328	ARTHRITIS AND RHEUMA	
Anon	2000	10	1951	EXPERT OPINION ON TH	
Boehringer Ingelheim Ph	2002			WO 0207772 A	HCAPLUS
Hatoum-Makdad, H	2003			WO 03068223 A	HCAPLUS
Madwed, J	2001	50	S175	IMFLAMMATION RESEARC	

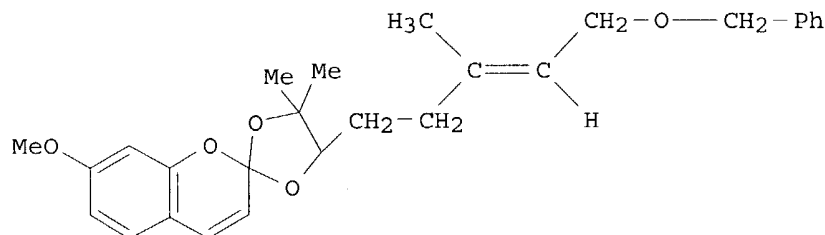
Madwed, J | 2001 | 50 | S184 | IMFLAMMATION RESEARC |  
 Smithkline Beecham Corp | 2001 | | | WO 0137837 A | HCAPLUS

L41 ANSWER 3 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3  
 ACCESSION NUMBER: 2004:252197 HCAPLUS  
 DOCUMENT NUMBER: 140:281350  
 ENTRY DATE: Entered STN: 26 Mar 2004  
 TITLE: Spiro compounds for inhibiting the first-pass effect  
 INVENTOR(S): Harris, James W.  
 PATENT ASSIGNEE(S): Bioavailability System, LLC, USA  
 SOURCE: U.S. Pat. Appl. Publ., 133 pp., Cont.-in-part of U.S.  
 Ser. No. 793,416.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 INT. PATENT CLASSIF.:  
 MAIN: A61K031-353  
 US PATENT CLASSIF.: 514453000  
 CLASSIFICATION: 1-2 (Pharmacology)  
 Section cross-reference(s): 28, 63  
 FAMILY ACC. NUM. COUNT: 5  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004058982	A1	20040325	US 2003-422848	20030425
US 6248776	B1	20010619	US 1999-251467	19990217
US 6476066	B1	20021105	US 2001-793416	20010227
PRIORITY APPLN. INFO.:			US 1999-251467	A3 19990217
			US 2001-793416	A2 20010227
			US 1997-56382P	P 19970826
			US 1997-997259	A2 19971223

## PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004058982	ICM	A61K031-353
	NCL	514453000
US 2004058982	ECLA	A23L001/30B; A23L002/06; A23L002/39; A61K031/352; A61K031/37; A61K035/78
US 6476066	ECLA	A23L001/30B; A23L002/06; A23L002/39; A61K031/35P; A61K031/37; A61K035/78; C07D493/10; C07D519/00
OTHER SOURCE(S):		MARPAT 140:281350
GRAPHIC IMAGE:		



## ABSTRACT:

Compns., methods, etc. for addressing the first-pass effect are presented. An example compound prepared was I. Also processing citrus oils to obtain the compds.

is given as examples as well as assessment of human cytochrome P 450-mediated biotransformation.

SUPPL. TERM: spiro compd first pass metab inhibition  
 INDEX TERM: Essential oils  
 ROLE: PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
 (citrus; spiro compds. for inhibiting the first-pass effect)  
 INDEX TERM: Drug delivery systems  
 (oral; spiro compds. for inhibiting the first-pass effect)  
 INDEX TERM: Human  
 Metabolism, animal  
 (spiro compds. for inhibiting the first-pass effect)  
 INDEX TERM: 674773-16-1P  
 ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (spiro compds. for inhibiting the first-pass effect)  
 INDEX TERM: 531-59-9, 7-Methoxycoumarin 55776-46-0, Benzyl 6,7-epoxygeranyl ether  
 ROLE: RCT (Reactant); RACT (Reactant or reagent)  
 (spiro compds. for inhibiting the first-pass effect)  
 INDEX TERM: 33069-62-4, Paclitaxel 114977-28-5, Docetaxel 127779-20-8, Saquinavir 161814-49-9, Amprenavir 174484-41-4, Tipranavir 206361-99-1, TMC114 226700-80-7, VX 175 300832-84-2, BILN 2061  
 461443-59-4 479543-46-9, VX-702 569364-34-7, VX-950 675184-03-9, VX 385 675184-27-7, HCV 371 675184-41-5, VP 50406  
 ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (spiro compds. for inhibiting the first-pass effect)

L41 ANSWER 4 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2004:325457 HCAPLUS  
 DOCUMENT NUMBER: 141:16899  
 ENTRY DATE: Entered STN: 22 Apr 2004  
 TITLE: In Vitro Resistance Studies of Hepatitis C Virus Serine Protease Inhibitors, VX-950 and **BILN 2061**: structural analysis indicates different resistance mechanisms  
 AUTHOR(S): Lin, Chao; Lin, Kai; Luong, Yu-Ping; Rao, B. Govinda; Wei, Yun-Yi; Brennan, Debra L.; Fulghum, John R.; Hsiao, Hsun-Mei; Ma, Sue; Maxwell, John P.; Cottrell, Kevin M.; Perni, Robert B.; Gates, Cynthia A.; Kwong, Ann D.  
 CORPORATE SOURCE: Vertex Pharmaceuticals Inc., Cambridge, MA, 02139, USA  
 SOURCE: Journal of Biological Chemistry (2004), 279(17), 17508-17514  
 CODEN: JBCHA3; ISSN: 0021-9258  
 PUBLISHER: American Society for Biochemistry and Molecular Biology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 CLASSIFICATION: 1-3 (Pharmacology)  
 ABSTRACT: We have used a structure-based drug design approach to identify small mol.

inhibitors of the hepatitis C virus (HCV) NS3-4A protease as potential candidates for new anti-HCV therapies. VX-950 is a potent NS3-4A protease inhibitor that was recently selected as a clin. development candidate for hepatitis C treatment. In this report, we describe in vitro resistance studies using a subgenomic replicon system to compare VX-950 with another HCV NS3-4A protease inhibitor, **BILN 2061**, for which the Phase I clin. trial results were reported recently. Distinct drug-resistant substitutions of a single amino acid were identified in the HCV NS3 serine protease domain for both inhibitors. The resistance conferred by these mutations was confirmed by characterization of the mutant enzymes and replicon cells that contain the single amino acid substitutions. The major **BILN \*\*\*2061\*\*\*** -resistant mutations at Asp168 are fully susceptible to VX-950, and the dominant resistant mutation against VX-950 at Ala156 remains sensitive to **\*\*\*BILN\*\*\* 2061**. Modeling anal. suggests that there are different mechanisms of resistance to VX-950 and **BILN 2061**.

SUPPL. TERM: hepatitis C virus serine protease antiviral resistance VX950  
BILN2061

INDEX TERM: Drug resistance  
Structure-activity relationship  
(antiviral; structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

INDEX TERM: Antiviral agents  
(resistance to; structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

INDEX TERM: Antiviral agents  
Hepatitis C virus  
Molecular modeling  
(structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

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INDEX TERM: Viral RNA  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
(structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

INDEX TERM: 56-41-7, L-Alanine, biological studies 70-47-3, L-Asparagine, biological studies  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
(mutation; structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

INDEX TERM: 149885-80-3, NS3 serine protease  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
(structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

INDEX TERM: **300832-84-2, BILN 2061**  
569364-34-7, VX-950  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(structure-activity relationship and in vitro antiviral

resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and BILN 2061)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD.

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Babine, R	2002			WO 0218369	HCAPLUS
Bartenschlager, R	1993	67	3835	J Virol	HCAPLUS
Bartenschlager, R	1995	69	7519	J Virol	HCAPLUS
Blight, K	1998	3	71	Antiviral Ther	MEDLINE
Blight, K	2000	290	1972	Science	HCAPLUS
Chander, G	2002	36	S135	Hepatology	

Davis, G	1998	339	1493	N Engl J Med	HCAPLUS
De Francesco, R	2003	58	1	Antiviral Res	HCAPLUS
Di Marco, S	2000	275	7152	J Biol Chem	HCAPLUS
Failla, C	1995	69	1769	J Virol	HCAPLUS
Grakoui, A	1993	67	1385	J Virol	HCAPLUS
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Hirsch, M	2003	37	113	Clin Infect Dis	
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Lamarre, D	2003	426	186	Nature	HCAPLUS
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Morrison, J	1969	185	269	Biochim Biophys Acta	HCAPLUS
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Tanji, Y	1995	69	1575	J Virol	HCAPLUS
Tomei, L	1993	67	4017	J Virol	HCAPLUS
Trozzi, C	2003	77	3669	J Virol	HCAPLUS
Tsantrizos, Y	2003	42	1356	Angew Chem Int Ed En	HCAPLUS
Wasley, A	2000	20	1	Semin Liver Dis	MEDLINE
Yao, N	1999	7	1353	Struct Fold Des	HCAPLUS

L41 ANSWER 5 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2004:468978 HCAPLUS

DOCUMENT NUMBER: 141:220806

ENTRY DATE: Entered STN: 10 Jun 2004

TITLE: Mutations conferring resistance to a potent hepatitis C virus serine protease inhibitor in vitro

AUTHOR(S): Lu, Liangjun; Pilot-Matias, Tami J.; Stewart, Kent D.; Randolph, John T.; Pithawalla, Ron; He, Wenping; Huang, Peggy P.; Klein, Larry L.; Mo, Hongmei; Molla, Akhteruzzaman

CORPORATE SOURCE: Antiviral Research, Global Pharmaceutical Research and Development, Abbott Park, IL, USA

SOURCE: Antimicrobial Agents and Chemotherapy (2004), 48(6), 2260-2266

CODEN: AMACQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

CLASSIFICATION: 7-5 (Enzymes)

Section cross-reference(s): 1, 10

## ABSTRACT:

**BILN 2061** is a novel, specific hepatitis C virus (HCV) NS3 serine protease inhibitor discovered by Boehringer Ingelheim that has shown potent activity against HCV replicons in tissue culture and is currently under clin. investigation for the treatment of HCV infection. The poor fidelity of the HCV RNA-dependent RNA polymerase will likely lead to the development of

drug-resistant viruses in treated patients. The development of resistance to \*\*\*BILN\*\*\* 2061 was studied by the in vitro passage of HCV genotype 1b replicon cells in the presence of a fixed concentration of the drug. Three weeks posttreatment, four colonies were expanded for genotypic and phenotypic characterization. The 50% inhibitory concns. of BILN 2061 for these colonies were 72- to 1228-fold higher than that for the wild-type replicon. Sequencing of the individual colonies identified several mutations in the NS3 serine protease gene. Mol. clones containing the single amino acid substitution A156T, R155Q, or D168V resulted in 357-fold, 24-fold, and 144-fold redns. in susceptibility to BILN 2061, resp., compared to the level of susceptibility shown by the wild-type replicon. Modeling studies indicate that all three of these residues are located in close proximity to the inhibitor binding site. These findings, in addition to the three-dimensional structure anal. of the NS3/NS4A serine protease inhibitor complex, provide a strategic guide for the development of next-generation inhibitors of HCV NS3/NS4A serine protease.

SUPPL. TERM: NS3 protease mutation BILN 2061  
hepatitis C virus

INDEX TERM: Drug resistance  
(antiviral; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: Hepatitis C virus  
(genotype 1b; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: Enzyme functional sites  
(inhibitor-binding; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: Conformation  
Mutation  
(mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: Replicon  
(of hepatitis C virus; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: 74-79-3, L-Arginine, biological studies  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
(155; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: 56-41-7, L-Alanine, biological studies  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
(156; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: 56-84-8, L-Aspartic acid, biological studies  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
(168; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: 259216-22-3 259216-62-1 300832-84-2,  
BILN 2061  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
(mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: 149885-80-3, NS3-NS4A protease  
ROLE: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(wild type and mutant forms; mutations conferring

inhibitor resistance on hepatitis C virus serine  
protease)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS  
RECORD.

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Bartenschlager, R	1999	6	165	J Viral Hepat	MEDLINE
Bartenschlager, R	1994	68	5045	J Virol	HCAPLUS
Boehringer Ingelheim (C	2003			US 6534523 B1	HCAPLUS
Boehringer Ingelheim (C	2003			US 6608027 B1	HCAPLUS
Cicero, D	1999	289	385	J Mol Biol	HCAPLUS
Cornberg, M	2002	4	23	Curr Gastroenterol R	
De Francesco, R	2002			WO 0259321	
Di Marco, S	2000	275	7152	J Biol Chem	HCAPLUS
Failla, C	1995	69	1769	J Virol	HCAPLUS
Foy, E	2003	300	1145	Science	HCAPLUS
Grakoui, A	1993	67	1385	J Virol	HCAPLUS

Ikeda, M	2002	76	2997	J Virol	HCAPLUS
Kolykhalov, A	2000	74	2046	J Virol	HCAPLUS
Krieger, N	2001	75	4614	J Virol	HCAPLUS
Lamarre, D	2003	426	186	Nature	HCAPLUS
Llinas-Brunet, M	1998	8	1713	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	2000	10	2267	Bioorg Med Chem Lett	HCAPLUS
Lohmann, V	2001	75	1437	J Virol	HCAPLUS
Mo, H	2003	59	173	Antivir Res	HCAPLUS
Molla, A	1996	2	760	Nat Med	HCAPLUS
Narjes, F	2003	12	153	Expert Opin Investig	HCAPLUS
Neddermann, P	1997	378	469	Biol Chem	HCAPLUS
Pauwels, R	1988	20	309	J Virol Methods	HCAPLUS
Pizzi, E	1994	91	888	Proc Natl Acad Sci U	HCAPLUS
Steinkuhler, C	2001	8	919	Curr Med Chem	HCAPLUS
Trozzi, C	2003	77	3669	J Virol	HCAPLUS
Tsantrizos, Y	2003	42	1356	Angew Chem Int Ed En	HCAPLUS
Wright, M	2001	12	201	Antivir Chem Chemoth	HCAPLUS
Yan, Y	1998	7	837	Protein Sci	HCAPLUS
Yao, N	1999	7	1353	Struct Fold Des	HCAPLUS
Yi, M	2002	304	197	Virology	HCAPLUS

L41 ANSWER 6 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 2004:168624 HCAPLUS

DOCUMENT NUMBER: 140:350045

ENTRY DATE: Entered STN: 02 Mar 2004

TITLE: Structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**

AUTHOR(S): Llinas-Brunet, Montse; Bailey, Murray D.; Bolger, Gordon; Brochu, Christian; Faucher, Anne-Marie; Ferland, Jean Marie; Garneau, Michel; Ghiro, Elise; Gorys, Vida; Grand-Maitre, Chantal; Halmos, Ted; Lapeyre-Paquette, Nicole; Liard, Francine; Poirier, Martin; Rheume, Manon; Tsantrizos, Youla S.; Lamarre, Daniel

CORPORATE SOURCE: Departments of Chemistry and Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.

SOURCE: Journal of Medicinal Chemistry (2004), 47(7), 1605-1608

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

CLASSIFICATION: 1-3 (Pharmacology)

Section cross-reference(s): 34

#### ABSTRACT:

From the discovery of competitive hexapeptide inhibitors, potent and selective HCV NS3 protease macrocyclic inhibitors have been identified. Structure-activity relationship studies were performed focusing on optimizing the N-terminal carbamate and the aromatic substituent on the (4R)-hydroxyproline moiety. Inhibitors meeting the potency criteria in the cell-based assay and with improved oral bioavailability in rats were identified. **BILN \*\*\*2061\*\*\*** was selected as the best compound, the first NS3 protease inhibitor reported with antiviral activity in man.

SUPPL. TERM: antiviral design hepatitis C virus NS3 protease BILN2061 structure; macrocyclic tripeptide prepn HCV NS3 protease inhibitor antiviral structure

INDEX TERM: Structure-activity relationship  
(HCV protease-inhibiting; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: Tripeptides  
ROLE: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(macrocyclic; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: Antiviral agents  
Drug bioavailability  
Drug design  
Human  
Peptidomimetics  
(structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: Macrocyclic compounds  
ROLE: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: 300832-84-2P  
ROLE: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(**BILN 2061**; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

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INDEX TERM: 9001-92-7P, Protease  
ROLE: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(HCV NS3 protease; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: 463-77-4, Carbamic acid, properties  
ROLE: PRP (Properties)  
(N-terminal; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: 51-35-4, Hydroxyproline  
ROLE: PRP (Properties)  
(moiety; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: 300832-73-9P  
ROLE: PAC (Pharmacological activity); PKT

(Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation) (structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: 300831-82-7P 300831-83-8P 300832-25-1P 300832-37-5P  
300832-38-6P 300832-40-0P 300832-44-4P 300832-51-3P  
300832-53-5P 300832-55-7P 300832-56-8P 300832-60-4P  
300832-64-8P 300832-66-0P 300832-67-1P 300832-71-7P  
300832-72-8P 300832-74-0P 300832-83-1P 300832-85-3P  
579472-70-1P 652160-88-8P 652160-90-2P

ROLE: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: 82121-05-9D, 4-Hydroxy-7-methoxyquinoline, 2-substituted derivs.

ROLE: RCT (Reactant); RACT (Reactant or reagent) (structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD.

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Choo, Q	1989	244	359	Science	HCAPLUS
Cornberg, M	2002	4	23	Curr Gastroenterol R	
Denissen, J	1995	23	185	Drug Metab Dispos	
Goudreau, N	2004	47	123	J Med Chem	HCAPLUS
Greene, T	1999		518	Protective Groups in	
Hagedorn, C	2000	242		Curr Top Microbiol I	HCAPLUS
Hepatitis, C	1996	71	346	Wkly Epidemiol Rec	
Kolykhalov, A	2000	74	2046	J Virol	HCAPLUS
Lamarre, D	2003	426	186	Nature	HCAPLUS
Laplante, S	2000	10	2271	Bioorg Med Chem Lett	HCAPLUS
Laplante, S	1999	274	18618	J Biol Chem	HCAPLUS
Lesk, A	1996	258	501	J Mol Biol	HCAPLUS
Lipinski, C	1997	1-3	3	Adv Drug Delivery Re	
Llinas-Brunet, M	1998	8	1713	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	1998	8	2719	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	2000	10	2267	Bioorg Med Chem Lett	HCAPLUS
Pause, A	2003	278	20374	J Biol Chem	HCAPLUS
Poupart, M	2001	66	4743	J Org Chem	HCAPLUS
Rancourt, J				J Med Chem, in press	
Reed, K	2000	242	55	Curr Top Microbiol I	HCAPLUS
Steinkuhler, C	1998	37	8899	Biochemistry	MEDLINE
Steinkuhler, C	2001	8	919	Curr Med Chem	HCAPLUS
Tsantrizos, Y	2003			US 6608027 B1	HCAPLUS
Tsantrizos, Y	2003	42	1356	Angew Chem, Int Ed	HCAPLUS
Tsantrizos, Y				Manuscript in prepar	
Yoakim, C	2003		473	Synlett	HCAPLUS

L41 ANSWER 7 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:392478 HCAPLUS

DOCUMENT NUMBER: 140:400031

ENTRY DATE: Entered STN: 14 May 2004

TITLE: Macrocyclic compound-containing compositions for the treatment of infection by Flaviviridae viruses

INVENTOR(S): Lamarre, Daniel; Lagace, Lisette

PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany

SOURCE: PCT Int. Appl., 57 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

INT. PATENT CLASSIF.:

MAIN: C07K005-08

SECONDARY: A61K038-05; A61K038-06; A61P031-14

CLASSIFICATION: 1-5 (Pharmacology)

Section cross-reference(s): 34, 63

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004039833	A1	20040513	WO 2003-CA1634	20031024
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,  
 GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,  
 LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,  
 OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,  
 TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ,  
 BY, KG, KZ, MD  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,  
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,  
 NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,  
 GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2002-421900P

P 20021029

US 2003-442769P

P 20030127

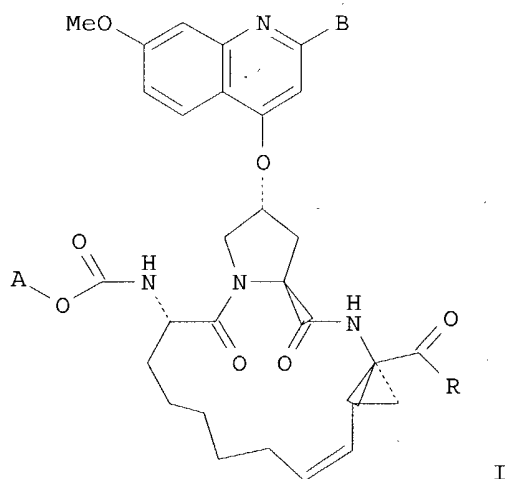
## PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004039833	ICM	C07K005-08
	ICS	A61K038-05; A61K038-06; A61P031-14

OTHER SOURCE(S):

MARPAT 140:400031

GRAPHIC IMAGE:



## ABSTRACT:

The invention relates to macrocyclic compds. I [A is alkyl or cycloalkyl; B is Ph or thiazolyl, which may be substituted by alkylamino or alkanoylamino; R is OH or NHSO<sub>2</sub>R<sub>2</sub>, where R<sub>2</sub> is (un)substituted alkyl, cycloalkyl or aryl] or their pharmaceutically-acceptable salts for the treatment of a mammal infected with a virus of the Flaviviridae family. Thus, IC<sub>50</sub> values for compound I [A is cyclopentyl, B is 2-(isopropylamino)-4-thiazolyl, R is OH] against HCV NS3-NS4A protease are shown graphically.

## SUPPL. TERM:

macrocyclic peptide treatment Flaviviridae virus; hepatitis C virus protease inhibitor macrocyclic peptide

## INDEX TERM:

Peptides, biological studies

ROLE: PAC (Pharmacological activity); THU (Therapeutic use);

BIOL (Biological study); USES (Uses)

(cyclic; macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

## INDEX TERM:

Antiviral agents

Flaviviridae

Hepatitis C virus

Hepatitis GB virus B  
(macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

INDEX TERM: Macrocytic compounds  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use);  
BIOL (Biological study); USES (Uses)  
(macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

INDEX TERM: Infection  
(viral; macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

INDEX TERM: 149885-80-3  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
(macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

INDEX TERM: 300831-83-8 300832-25-1 **300832-84-2**  
552335-24-7 681145-23-3 681145-24-4  
ROLE: PAC (Pharmacological activity); THU (Therapeutic use);  
BIOL (Biological study); USES (Uses)  
(macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

INDEX TERM: 688867-90-5 688867-91-6 688867-95-0 688867-96-1  
688867-98-3 688867-99-4 688868-00-0 688868-01-1  
688868-02-2 688868-03-3  
ROLE: PRP (Properties)  
(unclaimed nucleotide sequence; macrocyclic compound-containing compns. for the treatment of infection by Flaviviridae viruses)

INDEX TERM: 688867-92-7 688867-93-8 688867-94-9 688867-97-2  
ROLE: PRP (Properties)  
(unclaimed protein sequence; macrocyclic compound-containing compns. for the treatment of infection by Flaviviridae viruses)

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INDEX TERM: 259221-97-1 688747-48-0 688868-04-4 688868-05-5  
688868-06-6 688868-07-7 688868-08-8 688868-09-9  
688868-10-2 688868-11-3 688868-12-4 688868-13-5  
ROLE: PRP (Properties)  
(unclaimed sequence; macrocyclic compound-containing compns. for the treatment of infection by Flaviviridae viruses)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S): (1) Boehringer Ingelheim Ca Ltd; WO 0059929 A 2000 HCAPLUS  
(2) Boehringer Ingelheim Pharma; WO 03066103 A 2003 HCAPLUS  
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(5) Buchen-Osmond, C; www.ncbi.nlm.nih.gov/ICTVdb/ICTVdB/00.026.0.03.htm 2003, P1  
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(7) Llinas-Brunet, M; WO 03064455 A 2003 HCAPLUS  
(8) Squibb Bristol Myers Co; WO 03053349 A 2003 HCAPLUS

## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Boehringer Ingelheim Ca	2000			WO 0059929 A	HCAPLUS

Boehringer Ingelheim Ph	2003		WO 03066103 A	HCAPLUS
Buchen-Osmond, C	2003	1	www.ncbi.nlm.nih.gov	
Buchen-Osmond, C	2003	1	www.ncbi.nlm.nih.gov	
Buchen-Osmond, C	2003	1	www.ncbi.nlm.nih.gov	
Buchen-Osmond, C	2003	1	www.ncbi.nlm.nih.gov	
Llinas-Brunet, M	2003		WO 03064455 A	HCAPLUS
Squibb Bristol Myers Co	2003		WO 03053349 A	HCAPLUS

L41 ANSWER 8 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:370958 HCAPLUS

DOCUMENT NUMBER: 140:357673

ENTRY DATE: Entered STN: 07 May 2004

TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus

INVENTOR(S): Llinas-Brunet, Montse; Bailey, Murray D.

PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.h., Germany

SOURCE: PCT Int. Appl., 40 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

INT. PATENT CLASSIF.:

MAIN: C07K005-08

SECONDARY: A61K038-06

CLASSIFICATION: 34-3 (Amino Acids, Peptides, and Proteins)

Section cross-reference(s): 1, 7

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037855	A1	20040506	WO 2003-CA1604	20031020
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:	US 2002-421414P	P	20021025
	US 2002-433820P	P	20021216
	US 2003-442768P	P	20030127

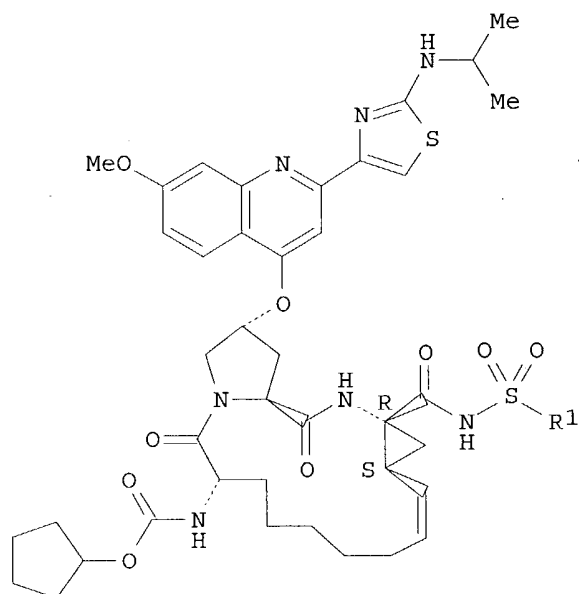
PATENT CLASSIFICATION CODES:

PATENT NO. CLASS PATENT FAMILY CLASSIFICATION CODES

WO 2004037855	ICM	C07K005-08
	ICS	A61K038-06

OTHER SOURCE(S): MARPAT 140:357673

GRAPHIC IMAGE:



I

## ABSTRACT:

Macrocyclic peptides I [R1 is (un)substituted alkyl, cycloalkyl, alkylcycloalkyl, aryl or heteroaryl] or their pharmaceutically-acceptable salts were prepared as inhibitors of the hepatitis C virus (HCV) NS3 protease. Thus, I (R = Me) was prepared by a multistep sequence involving peptide coupling, olefin metathesis to form the macrocycle and methanesulfonamidation.

SUPPL. TERM: macrocyclic peptide prepn inhibitor hepatitis C virus protease

INDEX TERM: Peptides, preparation

ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(cyclic; preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: Hepatitis C virus

(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: Interferons

ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

( $\alpha$ , pharmaceutical agents; preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 36791-04-5, Ribavirin

ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmaceutical agent; preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 149885-80-3, NS3 protease

ROLE: BSU (Biological study, unclassified); BIOL (Biological study)

(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 552335-24-7P 681145-23-3P 681145-24-4P 681145-25-5P  
681145-26-6P 681145-27-7P 681145-28-8P 681145-29-9P

681145-30-2P 681145-32-4P 681145-33-5P 681145-34-6P  
 681145-35-7P 681145-36-8P 681145-37-9P 681145-38-0P  
 681145-39-1P 681145-40-4P 681145-41-5P 681145-42-6P  
 ROLE: PAC (Pharmacological activity); SPN (Synthetic  
 preparation); THU (Therapeutic use); BIOL (Biological  
 study); PREP (Preparation); USES (Uses)

(preparation of macrocyclic peptides active against the  
 hepatitis C virus)

INDEX TERM: 96-41-3, Cyclopentanol 98-10-2, Benzenesulfonamide  
 1068-90-2, Diethyl acetamidomalonate 1719-76-2,  
 Isopropylthiourea 3144-09-0, Methanesulfonamide  
 13726-69-7 85866-02-0, 7 Octene 1 2 diol 154350-29-5,  
 Cyclopropanesulfonamide 259214-73-8 681260-04-8  
 ROLE: RCT (Reactant); RACT (Reactant or reagent)

(preparation of macrocyclic peptides active against the  
 hepatitis C virus)

INDEX TERM: 17206-61-0P, 6 Heptenal 54681-67-3P 300831-19-0P  
 300831-20-3P 300831-21-4P 300831-45-2P 300831-46-3P  
 300831-72-5P 300831-74-7P 300831-75-8P 300831-76-9P  
 300831-77-0P **300832-84-2P** 572922-89-5P  
 572922-90-8P 572922-91-9P 681145-21-1P 681145-22-2P  
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP

(Preparation); RACT (Reactant or reagent)  
 (preparation of macrocyclic peptides active against the  
 hepatitis C virus)

L41 ANSWER 9 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:590266 HCAPLUS

DOCUMENT NUMBER: 141:184653

ENTRY DATE: Entered STN: 25 Jul 2004

TITLE: Sensitivity of NS3 serine proteases from hepatitis C  
 virus genotypes 2 and 3 to the inhibitor **BILN**  
**2061**

AUTHOR(S): Thibeault, Diane; Bousquet, Christiane; Gingras, Rock;  
 Lagace, Lisette; Maurice, Roger; White, Peter W.;  
 Lamarre, Daniel

CORPORATE SOURCE: Department of Biological Sciences, Research and  
 Development, Boehringer Ingelheim (Canada) Ltd.,  
 Laval, QC, H7S 2G5, Can.

SOURCE: Journal of Virology (2004), 78(14), 7352-7359

CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

CLASSIFICATION: 1-5 (Pharmacology)

Section cross-reference(s): 3, 7, 10

#### ABSTRACT:

Hepatitis C virus (HCV) displays a high degree of genetic variability. Six  
 genotypes and more than 50 subtypes have been identified to date. In this  
 report, kinetic profiles were determined for NS3 proteases of genotypes 1a, 1b, 2ac,  
 2b, and 3a, revealing no major differences in activity. In vitro sensitivity  
 studies with **BILN 2061** showed a decrease in affinity for  
 proteases of genotypes 2 and 3 ( $K_i$ , 80 to 90 nM) compared to genotype 1 enzymes  
 ( $K_i$ , 1.5 nM). To understand the reduced sensitivity of genotypes 2 and 3 to  
 \*\*\***BILN**\*\*\* **2061**, active-site residues in the proximity of the  
 inhibitor binding site were replaced in the genotype-1b enzyme with the  
 corresponding genotype-2b or -3a residues. The replacement of five residues at  
 positions 78, 79, 80, 122, and 132 accounted for most of the reduced  
 sensitivity of genotype 2b, while replacement of residue 168 alone could  
 account for the reduced sensitivity of genotype 3a. **BILN**

\*\*\*2061\*\*\* remains a potent inhibitor of these non-genotype-1 NS3-NS4A proteins, with Ki values below 100 nM. This in vitro potency, in conjunction with the good pharmacokinetic data reported for humans, suggests that there is potential for **BILN 2061** as an antiviral agent for individuals infected with non-genotype-1 HCV.

SUPPL. TERM: hepatitis C virus NS3 serine protease variant BILN2061  
antiviral; enzyme active site mutation NS3NS4A heterodimer  
BILN2061 affinity genotype

INDEX TERM: Hepatitis  
(C; HCV genotypes 2 and 3 NS3 serine proteases sensitive  
to inhibitor **BILN 2061**)

INDEX TERM: Antiviral agents  
Genotypes  
Hepatitis C virus  
Human  
Mutation  
(HCV genotypes 2 and 3 NS3 serine proteases sensitive to  
inhibitor **BILN 2061**)

INDEX TERM: Proteins  
ROLE: BSU (Biological study, unclassified); PRP  
(Properties); BIOL (Biological study)  
(NS3-NS4A heterodimer; HCV genotypes 2 and 3 NS3 serine  
proteases sensitive to inhibitor **BILN 2061**)

INDEX TERM: Enzyme functional sites  
(active; HCV genotypes 2 and 3 NS3 serine proteases  
sensitive to inhibitor **BILN 2061**)

INDEX TERM: Drug resistance  
(antiviral; HCV genotypes 2 and 3 NS3 serine proteases  
sensitive to inhibitor **BILN 2061**)

INDEX TERM: Molecular association  
(effect of HCV NS3-NS4A genotype variation on NS3  
protease on BILN 2061affinity; HCV genotypes 2 and 3 NS3  
serine proteases sensitive to inhibitor **BILN 2061**)

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INDEX TERM: Enzyme kinetics  
(of inhibition, of NS3-NS4A heterodimer protein of  
genotypes 1, 2, and 3; HCV genotypes 2 and 3 NS3 serine  
proteases sensitive to inhibitor **BILN 2061**)

INDEX TERM: Antiviral agents  
(resistance to; HCV genotypes 2 and 3 NS3 serine  
proteases sensitive to inhibitor **BILN 2061**)

INDEX TERM: 149885-80-3, NS3 serine protease  
ROLE: BSU (Biological study, unclassified); PRP  
(Properties); BIOL (Biological study)  
(HCV genotypes 2 and 3 NS3 serine proteases sensitive to  
inhibitor **BILN 2061**)

INDEX TERM: **300832-84-2, BILN 2061**  
ROLE: DMA (Drug mechanism of action); PAC (Pharmacological  
activity); THU (Therapeutic use); BIOL (Biological study);  
USES (Uses)  
(HCV genotypes 2 and 3 NS3 serine proteases sensitive to  
inhibitor **BILN 2061**)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS  
RECORD.

REFERENCE(S): (1) Beyer, B; Proteins 2001, V43, P82 HCAPLUS  
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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Beyer, B	2001	43	82	Proteins	HCAPLUS
Bianchi, E	1996	237	239	Anal Biochem	HCAPLUS
Bodansky, M	1993			Peptide chemistry, 2	
Di Bisceglie, A	2002	36	S121	Hepatology	
Domingo, E	2002	82	39	Virus Res	HCAPLUS
Drake, J	1999	96	13910	Proc Natl Acad Sci U	HCAPLUS
Hoofnagle, J	2002	36	S21	Hepatology	
Kakiuchi, N	1995	210	1059	Biochem Biophys Res	HCAPLUS
Kim, J	1996	87	343	Cell	HCAPLUS
Koch, U	2001	40	631	Biochemistry	HCAPLUS
Kolykhalov, A	2000	74	2046	J Virol	HCAPLUS
Lamarre, D	2003	426	186	Nature	HCAPLUS
Laplante, S	1999	274	18618	J Biol Chem	HCAPLUS
Lin, C	1995	69	4373	J Virol	HCAPLUS
Llinas-Brunet, M	1998	8	1713	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	1998	8	2719	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	2000	10	2267	Bioorg Med Chem Lett	HCAPLUS
Mondelli, M	1999	31	65	J Hepatol	

Muzammil, S	2003	42	631	Biochemistry	HCAPLUS
Neumann, A	1998	282	103	Science	HCAPLUS
Pause, A	2003	278	20374	J Biol Chem	HCAPLUS
Pawlotsky, J	2003	7	45	Clin Liver Dis	
Reed, K	2000	242	55	Curr Top Microbiol I	HCAPLUS
Simmonds, P	2001	82	693	J Gen Virol	HCAPLUS
Simmonds, P	1999	31	54	J Hepatol	
Steinhuhler, C	2001	8	919	Curr Med Chem	
Taliani, M	1996	240	60	Anal Biochem	HCAPLUS
Trozzi, C	2003	77	3669	J Virol	HCAPLUS
Tsantrizos, Y	2003			US 6608027 B1	HCAPLUS
Tsantrizos, Y	2003	42	1355	Angew Chem Int Ed	
Webster, G	2000	14	229	Bailliere's Clin Gas	MEDLINE
Wright-Minogue, J	2000	32	497	J Hepatol	HCAPLUS
Yan, Y	1998	7	837	Protein Sci	HCAPLUS

L41 ANSWER 10 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:580783 HCAPLUS

DOCUMENT NUMBER: 141:261053

ENTRY DATE: Entered STN: 21 Jul 2004

TITLE: Synthesis of **BILN 2061**, an HCV NS3  
Protease Inhibitor with Proven Antiviral Effect in  
Humans

AUTHOR(S): Faucher, Anne-Marie; Bailey, Murray D.; Beaulieu,  
Pierre L.; Brochu, Christian; Duceppe, Jean-Simon;  
Ferland, Jean-Marie; Ghiro, Elise; Gorys, Vida;  
Halmos, Ted; Kawai, Stephen H.; Poirier, Martin;  
Simoneau, Bruno; Tsantrizos, Youla S.; Llinas-Brunet,  
Montse

CORPORATE SOURCE: Chemistry Department, Boehringer Ingelheim (Canada)  
Ltd., Laval, QC, H7S 2G5, Can.

SOURCE: Organic Letters (2004), 6(17), 2901-2904  
CODEN: ORLEF7; ISSN: 1523-7060

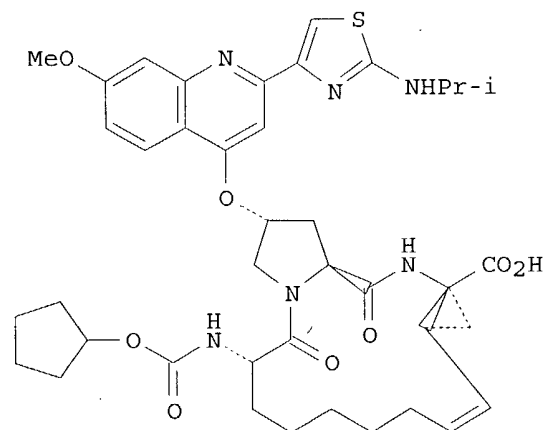
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

CLASSIFICATION: 34-3 (Amino Acids, Peptides, and Proteins)  
Section cross-reference(s): 1

GRAPHIC IMAGE:



## ABSTRACT:

The synthesis of **BILN 2061** (I), a hepatitis C virus (HCV) NS3 protease inhibitor with proven antiviral effect in humans, was accomplished in a convergent manner from four building blocks. The procedure described here was suitable for the preparation of multigram quantities of **BILN \*\*\*2061\*\*\*** for preclin. pharmacol. evaluation.

SUPPL. TERM: **BILN 2061** peptide macrocycle prepn  
antiviral agent human

INDEX TERM: Substitution reaction, nucleophilic  
(Mitsunobu; total synthesis of peptidyl macrocycle **BILN-2061**)

INDEX TERM: Cyclization  
(metathesis; total synthesis of peptidyl macrocycle **BILN-2061**)

INDEX TERM: Antiviral agents  
Hepatitis C virus  
Human  
(preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: Macrocyclic compounds  
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: Metathesis  
(ring-closing; total synthesis of peptidyl macrocycle **BILN-2061**)

INDEX TERM: Hydrogenation  
(stereoselective; total synthesis of peptidyl macrocycle **BILN-2061**)

INDEX TERM: Asymmetric synthesis and induction  
(total synthesis of peptidyl macrocycle **BILN-2061**)

INDEX TERM: Infection  
(viral; preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: 149885-80-3, NS3 protease  
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
(preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: 142184-30-3, [(COD)Rh(S,S)-Et-DuPHOS)]OTF 203714-71-0  
ROLE: CAT (Catalyst use); USES (Uses)  
(preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: **300832-84-2P**  
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: 1068-90-2 13726-69-7 50715-28-1 85866-02-0,

7-Octene-1,2-diol 259214-73-8 681260-04-8  
 ROLE: RCT (Reactant); RACT (Reactant or reagent)  
 (preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

## INDEX TERM:

17206-61-0P, 6-Heptenal 54681-67-3P 300831-20-3P  
 300831-21-4P 300831-45-2P 300831-46-3P 300831-72-5P  
 300831-74-7P 572922-89-5P 572922-91-9P 681145-22-2P  
 756894-33-4P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

## REFERENCE COUNT:

39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD.

## REFERENCE(S):

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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
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Bailey, M	2004			J Med Chem	
Beaulieu, P	2002	1	163	Curr Med Chem:Anti-I	HCAPLUS
Benhamou, Y	2002	36	304A	Hepatology, Abst 563	
Burk, M	1998	120	657	J Am Chem Soc	HCAPLUS
Burk, M	1997	62	7054	J Org Chem	HCAPLUS
Choo, Q	1989	244	359	Science	HCAPLUS
Cornberg, M	2002	4	23	Curr Gastroenterol R	
Furstner, A	2000	39	3012	Angew Chem, Int Ed	HCAPLUS
Goudreau, N	2004	47	123	J Med Chem	HCAPLUS
Hagedorn, C	2000	242		Curr Top Microbiol I	HCAPLUS
Hengartner, U	1979	44	3741	J Org Chem	HCAPLUS
Hinrichsen, H	2002	36	297A	Hepatology, Abst 866	
Huang, J	1999	121	2674	J Am Chem Soc	HCAPLUS
Johnson, J	1942	1	210	Organic Reactions, C	
Kingsbury, J	1999	121	791	J Am Chem Soc	HCAPLUS
Knorr, R	1989	30	1927	Tetrahedron Lett	HCAPLUS
Kolykalov, A	2000	74	2046	J Virol	
Lamarre, D	2003	426	186	Nature	HCAPLUS
Laplante, S	2000	10	2271	Bioorg Med Chem Lett	HCAPLUS
Liu, K	1979	31	80	Taiwan Yaoxue Zazhi	HCAPLUS
Llinas-Brunet, M	2000			US 6323180 B1	HCAPLUS
Llinas-Brunet, M	1998	8	1713	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	2000	10	2267	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	2004	47	1605	J Med Chem	HCAPLUS
Miller, S	1996	118	9606	J Am Chem Soc	HCAPLUS
Mitsunobu, O	1981		1	Synthesis	HCAPLUS
Pham, T	1994	59	3676	J Org Chem	HCAPLUS
Poirier, M				Manuscript in prepar	
Poupart, M	2001	66	4743	J Org Chem	HCAPLUS
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Reed, K	2000	242	55	Curr Top Microbiol I	HCAPLUS
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Schechter, I	1967	27	157	Biochem Biophys Res	HCAPLUS
Scholl, M	1999	40	2247	Tetrahedron Lett	HCAPLUS
Schrock, R	2003	42	4592	Angew Chem, Int Ed	HCAPLUS
Steinkuler, C	1998	37	8899	Biochemistry	
Trnka, T	2001	34	18	Acc Chem Res	HCAPLUS
Tsantrisos, Y	2003			US 6608027	HCAPLUS
Tsantrizos, Y	2003	42	1355	Angew Chem, Int Ed	

L41 ANSWER 11 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:561437 HCAPLUS

ENTRY DATE: Entered STN: 14 Jul 2004

TITLE: **BILN 2061:** a major step toward new therapeutic strategies in hepatitis CAUTHOR(S): Asselah, Tarik; Marcellin, Patrick  
CORPORATE SOURCE: Service d'HepatoLOGIE, INSERM U 481, Centre de Recherche Claude Bernard sur les Hepatites Virales, Clichy, 92110, Fr.

SOURCE: Journal of Hepatology (2004), 41(1), 178-181

CODEN: JOHEEC; ISSN: 0168-8278

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

CLASSIFICATION: 1 (Pharmacology)  
 ABSTRACT: Unavailable  
 REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S): (1) Anon; Hepatology 2002, V36  
 (2) Anon; J Hepatol 1999, V31, P1  
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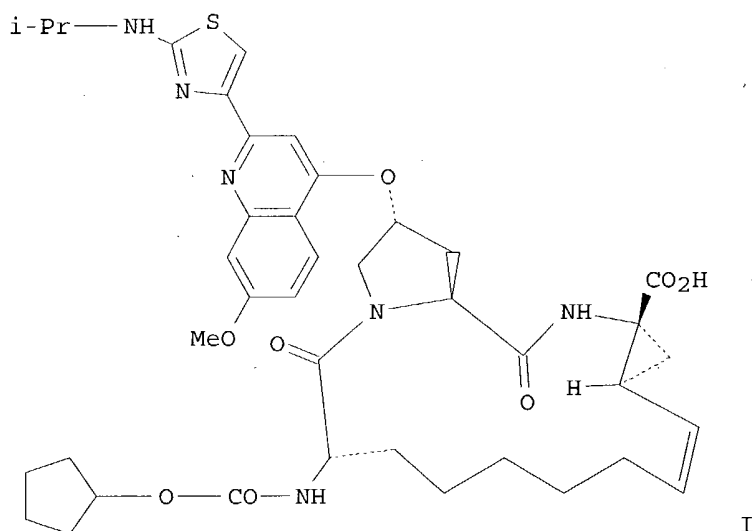
## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
=====	=====	=====	=====	=====	=====
Anon	2002	36		Hepatology	
Anon	1999	31	1	J Hepatol	
Benhamou, Y	2002	36		Hepatology	
Blight, K	2000	290	1972	Science	HCAPLUS
Dhumeaux, D	2003	52	1784	Gut	MEDLINE
Foy, E	2003	300	1145	Science	HCAPLUS
Hinrichsen, H	2002	36		Hepatology	
Kato, T	2003	125	1808	Gastroenterology	HCAPLUS
Kim, J	1996	87	343	Cell	HCAPLUS
Lamarre, D	2003	426	186	Nature	HCAPLUS
Lin, C	2004	279	17508	J Biol Chem	HCAPLUS
Lohmann, V	1999	285	110	Science	HCAPLUS
Love, R	1996	87	331	Cell	HCAPLUS
Marcellin, P	2002	36	S47	Hepatology	
Narjes, H	2002	36	800	Hepatology	
Pause, A	2003	278	20374	J Biol Chem	HCAPLUS
Reiser, M	2003	38		Hepatology	
Steinkuhler, C	1998	37	8899	Biochemistry	MEDLINE
Trozzi, C	2003	77	3669	J Virol	HCAPLUS

L41 ANSWER 12 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2003:633516 HCAPLUS  
 DOCUMENT NUMBER: 139:185670  
 ENTRY DATE: Entered STN: 15 Aug 2003  
 TITLE: Pharmaceutical compositions for hepatitis C viral protease inhibitors  
 INVENTOR(S): Chen, Shirlynn; Mei, Xiaohui  
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA  
 SOURCE: PCT Int. Appl., 73 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 INT. PATENT CLASSIF.:

MAIN: A61K047-18  
 SECONDARY: A61K038-05; A61K038-06  
 CLASSIFICATION: 63-6 (Pharmaceuticals)  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003066103	A1	20030814	WO 2003-US3380	20030205
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003195228	A1	20031016	US 2003-357919	20030204
PRIORITY APPLN. INFO.:			US 2002-355694P	P 20020207
PATENT CLASSIFICATION CODES:				
PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES		
WO 2003066103	ICM	A61K047-18		
	ICS	A61K038-05; A61K038-06		
OTHER SOURCE(S):		MARPAT 139:185670		
GRAPHIC IMAGE:				



# ABSTRACT:

Disclosed are pharmaceutical compns. of hepatitis C viral protease inhibitors having improved bioavailability, and methods of using these compns. for inhibiting the replication of the hepatitis C virus (HCV) and for the treatment of an HCV infection. These compns. include co-solvent systems, lipid based

systems, solid dispersions and granulations, and all comprise the hepatitis C viral protease inhibitor, at least one pharmaceutically acceptable amine and optionally one or more addnl. ingredients. A composition contained I 4, tromethamine 3.2, water 44.8, ethanol 21.3, and propylene glycol 26.7 weight/weight%.

SUPPL. TERM: hepatitis C viral protease inhibitor pharmaceutical  
 INDEX TERM: Drug delivery systems  
 (capsules; pharmaceutical compns. for hepatitis C viral protease inhibitors)

INDEX TERM: Castor oil  
 ROLE: MOA (Modifier or additive use); THU (Therapeutic use);  
 BIOL (Biological study); USES (Uses)  
 (ethoxylated; pharmaceutical compns. for hepatitis C viral protease inhibitors)

INDEX TERM: Antioxidants  
 Drug bioavailability  
 (pharmaceutical compns. for hepatitis C viral protease inhibitors)

INDEX TERM: Polyoxyalkylenes, biological studies  
 ROLE: MOA (Modifier or additive use); THU (Therapeutic use);  
 BIOL (Biological study); USES (Uses)  
 (pharmaceutical compns. for hepatitis C viral protease inhibitors)

INDEX TERM: Drug delivery systems  
 (powders; pharmaceutical compns. for hepatitis C viral protease inhibitors)

INDEX TERM: Drug delivery systems  
 (tablets; pharmaceutical compns. for hepatitis C viral protease inhibitors)

INDEX TERM: 9001-92-7, Protease  
 ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
 (hepatitis C virus; pharmaceutical compns. for hepatitis C viral protease inhibitors)

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INDEX TERM: ~~300832-84-2~~  
 ROLE: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (pharmaceutical compns. for hepatitis C viral protease inhibitors)

INDEX TERM: 57-55-6, Propylene glycol, biological studies 64-17-5, Ethanol, biological studies 77-86-1, Tris 151-21-3, Sodium lauryl sulfate, biological studies 7732-18-5, Water, biological studies 9002-96-4,  $\alpha$ -Tocopheryl polyethylene glycol succinate 9003-39-8, Pvp 25322-68-3, Peg 106392-12-5, Oxirane, polymer with methyloxirane, block  
 ROLE: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (pharmaceutical compns. for hepatitis C viral protease inhibitors)

INDEX TERM: 300832-64-8 300832-66-0 300832-67-1 300832-69-3  
 300832-70-6 300832-71-7 300832-72-8 300832-73-9  
 300832-74-0 300832-76-2 300832-77-3 300832-78-4  
 300832-79-5 300832-80-8 300832-81-9 300832-83-1  
 300832-85-3 300832-86-4 572922-86-2 572922-94-2  
 577965-78-7 577965-82-3 577965-83-4  
 ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (pharmaceutical compns. for hepatitis C viral protease inhibitors)

213

inhibitors)  
 REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S): (1) Boehringer Ingelheim Ca Ltd; WO 0059929 A 2000 HCAPLUS  
 (2) Morozowich, W; WO 9906044 A 1999 HCAPLUS

## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Boehringer Ingelheim Ca	2000			WO 0059929 A	HCAPLUS
Morozowich, W	1999			WO 9906044 A	HCAPLUS

L41 ANSWER 13 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:511084 HCAPLUS

DOCUMENT NUMBER: 139:69527

ENTRY DATE: Entered STN: 04 Jul 2003

TITLE: Preparation of macrocyclic compounds as inhibitors of hepatitis C virus

INVENTOR(S): Campbell, Jeffrey Allen; Good, Andrew Charles

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: PCT Int. Appl., 225 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

INT. PATENT CLASSIF.:

MAIN: A61K

CLASSIFICATION: 34-3 (Amino Acids, Peptides, and Proteins)

Section cross-reference(s): 1, 63

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003053349	A2	20030703	WO 2002-US39926	20021213
WO 2003053349	A3	20040115		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2004038872	A1	20040226	US 2002-317451	20021212
EP 1455809	A2	20040915	EP 2002-795860	20021213
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK			
PRIORITY APPLN. INFO.:			US 2001-344080P	P 20011220
			US 2002-382103P	P 20020520
			WO 2002-US39926	W 20021213

## PATENT CLASSIFICATION CODES:

PATENT NO. CLASS PATENT FAMILY CLASSIFICATION CODES

WO 2003053349 ICM A61K  
 OTHER SOURCE(S): MARPAT 139:69527

GRAPHIC IMAGE:

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

ABSTRACT:

The invention relates to macrocyclic compds. I [R1 = (cyclo)alkyl; R2 = H, halo, alkyl, alkoxy, cycloalkoxy, (un)substituted aryl or heterocyclyl; R3 = H, halo, CF3, alkoxy, cycloalkoxy; R4 = NH2 or NHR6, where R6 is alkanoyl, alkylaminocarbonyl, or carbalkoxy; Q is a 3-9 atom (un)saturated alkylene chain optionally containing 1-3 heteroatoms O, S, SO, or SO2], including methods for their synthesis and use in pharmaceutical compns. for therapeutic or prophylactic prevention or treatment of hepatitis C virus (HCV) infection. Thus, 3,13-diazatricyclo[11.3.0.04,6]hexadec-7-ene derivative II was prepared by a multistep procedure and assayed for inhibition of HCV NS3/4A protease (IC50 < 5  $\mu$ M).

SUPPL. TERM: macrocyclic peptide prepn inhibitor hepatitis C virus  
 INDEX TERM: Peptides, preparation  
 ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (cyclic; preparation of macrocyclic compds. as inhibitors of hepatitis C virus)  
 INDEX TERM: Antiviral agents  
 Hepatitis C virus  
 Human  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)  
 INDEX TERM: Macrocyclic compounds  
 ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)  
 INDEX TERM: Infection  
 (viral; preparation of macrocyclic compds. as inhibitors of hepatitis C virus)  
 INDEX TERM: 552334-90-4P 552334-92-6P 552334-94-8P 552334-96-0P  
 552334-98-2P 552334-99-3P  
 ROLE: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)  
 INDEX TERM: 552334-91-5P 552334-93-7P 552334-95-9P 552334-97-1P  
 ROLE: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)  
 INDEX TERM: 259214-55-6P 259217-95-3P  
 ROLE: BPN (Biosynthetic preparation); RCT (Reactant); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)  
 INDEX TERM: 300831-62-3P 300831-63-4P 300831-83-8P 445305-87-3P

445305-88-4P 445305-89-5P 552335-25-8P 552335-26-9P  
 552335-27-0P 552335-28-1P 552335-29-2P 552335-30-5P  
 552335-31-6P 552335-32-7P 552335-33-8P 552335-34-9P  
 552335-35-0P

ROLE: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 9004-06-2, Elastase 9004-07-3, Chymotrypsin 9047-22-7, Cathepsin b 149885-80-3, Ns3 protease  
 ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 213316-49-5P  
 ROLE: CPS (Chemical process); PEP (Physical, engineering or chemical process); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 552335-03-2P 552335-04-3P 552335-05-4P 552335-21-4P  
 ROLE: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 552335-00-9P 552335-01-0P 552335-02-1P 552335-06-5P  
 552335-07-6P 552335-08-7P 552335-09-8P 552335-10-1P  
 552335-12-3P 552335-13-4P 552335-14-5P 552335-15-6P  
 552335-16-7P 552335-17-8P 552335-18-9P 552335-19-0P  
 552335-20-3P 552335-22-5P 552335-23-6P 552335-24-7P  
 ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 94-02-0, Ethyl benzoylacetate 100-52-7, Benzaldehyde, reactions 462-27-1, 2 Fluoroethyl chloroformate 536-90-3, m-Anisidine 563-80-4, 3 Methyl 2 butanone 611-35-8, 4 Chloroquinoline 623-33-6, Glycine ethyl ester hydrochloride 821-06-7, trans-1 4 Dibromo 2 butene 1119-51-3, 1 Bromo 4 pentene 1609-86-5, tert-Butyl isocyanate 1719-76-2, Isopropylthiourea 2033-24-1, Meldrum's acid 3144-09-0, Methanesulfonamide 4399-47-7, Cyclobutyl bromide 4910-62-7, Diazenedicarboxylic acid dipotassium salt 5239-82-7, Cyclopropylacetic acid 13726-69-7 16982-21-1 20412-38-8, Neopentyl chloroformate 23779-97-7 40216-83-9 50715-28-1, Cyclopentyl chloroformate 55757-46-5 69555-14-2 89641-80-5 102195-79-9 139631-62-2, Cyclopropanesulfonyl chloride 178153-11-2 204711-97-7 208522-13-8 259214-75-0 300831-21-4 552335-71-4 552335-72-5  
 ROLE: RCT (Reactant); RACT (Reactant or reagent)  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 19967-55-6P, 1 Bromo 3 methyl 2 butanone 40682-54-0P  
 42465-53-2P 82121-05-9P 154350-29-5P,

Cyclopropanesulfonamide 156589-82-1P 189816-04-4P  
 189816-05-5P 213699-52-6P 259214-37-4P 259214-54-5P  
 259214-56-7P 259214-64-7P 300830-83-5P 300831-06-5P  
 300831-07-6P 300831-08-7P 300831-33-8P 300831-81-6P  
 300831-89-4P 300832-25-1P 300832-47-7P  
**300832-84-2P** 445305-91-9P, Cyclobutanesulfonamide  
 552335-36-1P 552335-37-2P 552335-39-4P 552335-40-7P  
 552335-41-8P 552335-42-9P 552335-43-0P 552335-44-1P  
 552335-45-2P 552335-46-3P 552335-47-4P 552335-48-5P  
 552335-49-6P 552335-50-9P 552335-51-0P 552335-52-1P  
 552335-53-2P 552335-54-3P 552335-55-4P 552335-56-5P  
 552335-57-6P 552335-58-7P 552335-59-8P 552335-60-1P  
 552335-61-2P 552335-62-3P 552335-63-4P 552335-64-5P  
 552335-65-6P 552335-66-7P 552335-67-8P 552335-68-9P  
 552335-69-0P 552335-70-3P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 552335-38-3P

ROLE: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

L41 ANSWER 14 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:648255 HCAPLUS

DOCUMENT NUMBER: 139:197768

ENTRY DATE: Entered STN: 20 Aug 2003

TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus

INVENTOR(S): Tsantrizos, Youla S.; Cameron, Dale R.; Faucher, Anne-Marie; Ghio, Elise; Goudreau, Nathalie; Halmos, Teddy; Llinas-Brunet, Montse

PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.

SOURCE: U.S., 90 pp., Cont.-in-part of U.S. Ser. No. 542,675, abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

INT. PATENT CLASSIF.:

MAIN: A61K038-05

SECONDARY: A61K038-06; A61K038-12; C07K005-08; C07K005-12

US PATENT CLASSIF.: 514009000; 514010000; 514011000; 514018000; 514019000; 530317000; 530321000; 530331000; 540454000; 540455000

CLASSIFICATION: 34-3 (Amino Acids, Peptides, and Proteins)

Section cross-reference(s): 1, 15

FAMILY ACC. NUM. COUNT: 2

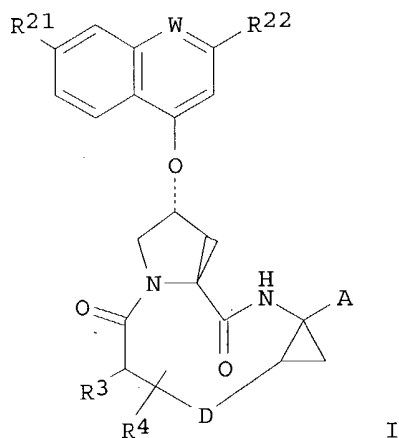
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6608027	B1	20030819	US 2001-760946	20010116
EP 1437362	A1	20040714	EP 2004-9264	20000403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY				
US 2004002448	A1	20040101	US 2003-358726	20030205
PRIORITY APPLN. INFO.:				
			US 1999-128011P	P 19990406
			US 2000-542675	B2 20000403
			EP 2000-913999	A3 20000403
			US 2001-760946	A1 20010116

## PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 6608027	ICM	A61K038-05
	ICS	A61K038-06; A61K038-12; C07K005-08; C07K005-12
	NCL	514009000; 514010000; 514011000; 514018000; 514019000; 530317000; 530321000; 530331000; 540454000; 540455000
US 6608027	ECLA	C07K005/06H2; C07K005/08A
US 2004002448	ECLA	C07K005/06H2; C07K005/08A
OTHER SOURCE(S):		MARPAT 139:197768

GRAPHIC IMAGE:



## ABSTRACT:

Macrocyclic peptides I [W = CH or N; R21 = H, halo, alkyl, cycloalkyl, haloalkyl, alkoxy, cycloalkoxy, hydroxy, or an amino group; R22 = H, halo, alkyl, cycloalkyl, haloalkyl, thioalkyl, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkyl, aryl or heteroaryl; R3 = hydroxy, NH2, aryl- or heteroarylamino, NHCOR32, CONHR32, CO2R32, where R32 is alkyl or cycloalkyl; D is a 5 to 10-atom saturated or unsatd. alkylene chain optionally containing one to three heteroatoms independently selected from: O, S, or NH or substituted imino; R4 = H or from one to three substituents at any carbon atom of chain D; A is an amide or carboxylic acid group or a pharmaceutically acceptable salt or ester; two diastereomers may exist at the cyclopropane moiety] were prepared which are active in-vitro and in cellular assays against the NS3 protease of the hepatitis C virus. Thus, macrocyclic peptide I [W = N; R21, R22, R4 = H; A = CO2H; R3CH-D = (S)-(Me3CO2CNH)CH(CH2)3CH:CH(CH2)2-E (syn to acid)] was prepared and showed IC50 > 0.1 μM in the full-length NS3-NS4A heterodimer protein fluorogenic assay.

SUPPL. TERM: cyclic peptide prepn hepatitis C virus inhibitor  
 INDEX TERM: Hepatitis C virus  
 Immunomodulators  
 (preparation of macrocyclic peptides active against the hepatitis C virus)  
 INDEX TERM: Macrocyclic compounds  
 Peptides, preparation  
 ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological

study); PREP (Preparation); USES (Uses)  
 (preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: Interferons  
 ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 37259-58-8, Serine protease  
 ROLE: BSU (Biological study, unclassified); BIOL (Biological study)  
 (preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 300831-32-7P 300831-33-8P 300831-34-9P 300831-79-2P  
 300831-80-5P 300831-81-6P 300831-82-7P 300831-83-8P  
 300831-84-9P 300831-85-0P 300831-86-1P 300831-87-2P  
 300831-88-3P 300831-89-4P 300831-90-7P 300831-91-8P  
 300831-92-9P 300831-93-0P 300831-94-1P 300831-95-2P  
 300831-96-3P 300831-97-4P 300831-98-5P 300831-99-6P  
 300832-00-2P 300832-01-3P 300832-02-4P 300832-03-5P  
 300832-04-6P 300832-05-7P 300832-06-8P 300832-07-9P  
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 300832-60-4P 300832-61-5P 300832-62-6P 300832-63-7P  
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 300832-99-9P 300833-00-5P 300833-01-6P 300833-02-7P  
 301188-00-1P 572922-86-2P 572922-94-2P 577965-82-3P  
 577965-83-4P  
 ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 62-56-6, Thiourea, reactions 78-39-7, Triethyl orthoacetate 79-22-1, Methyl chloroformate 98-88-4, Benzoyl chloride 105-56-6, Ethyl cyanoacetate 288-13-1, Pyrazole 288-32-4, Imidazole, reactions 333-20-0, Potassium thiocyanate 536-90-3, m-Anisidine 541-16-2, Di-tert-butyl malonate 543-27-1, Isobutyl chloroformate 563-80-4, 3-Methyl-2-butanone 590-42-1, tert-Butyl isothiocyanate 591-08-2, n-Acetylthiourea 598-52-7,

n-Methylthiourea 625-53-6, n-Ethylthiourea 696-59-3,  
 2,5-Dimethoxytetrahydrofuran 765-30-0, Cyclopropylamine  
 822-36-6, 4-Methylimidazole 934-60-1, 6-Methylpicolinic  
 acid 1003-03-8, Cyclopentylamine 1068-90-2, Diethyl  
 acetamidomalonate 1113-41-3, L-Penicillamine 1113-59-3,  
 3-Bromopyruvic acid 1119-51-3, 4-Pentenyl bromide  
 1719-76-2, Isopropylthiourea 2385-77-5 2592-18-9  
 2695-48-9, 8-Bromo-1-octene 3282-30-2, Pivaloyl chloride  
 4285-48-7 7554-65-6, 4-Methylpyrazole 10387-40-3,  
 Potassium thioacetate 13726-85-7 16982-21-1, Ethyl  
 thiooxamate 22059-22-9, Acetamidoxime 29681-39-8  
 50413-30-4 50715-28-1 82121-05-9, 4-Hydroxy-7-  
 methoxyquinoline 85866-02-0, 7-Octene-1,2-diol  
 90719-32-7 102195-79-9 113240-46-3, Malonic acid  
 monoallyl ester 126690-67-3 204711-97-7 259214-64-7  
 259214-73-8 300831-45-2 300831-47-4 300831-50-9  
 300831-58-7 300831-62-3 300831-65-6 300831-67-8  
 ROLE: RCT (Reactant); RACT (Reactant or reagent)

(preparation of macrocyclic peptides active against the  
 hepatitis C virus)

## INDEX TERM:

616-47-7P, 1-Methylimidazole 3350-20-7P 17206-61-0P,  
 6-Heptenal 19967-55-6P 20485-43-2P 27191-09-9P,  
 m-Anisidine hydrochloride 29082-92-6P 31642-67-8P,  
 8-Nonenoic acid 42465-53-2P 55327-87-2P,  
 Acetamidomalonic acid 56541-14-1P, n-Cyclopropylthiourea  
 56541-16-3P 70498-31-6P 72086-72-7P 79479-07-5P  
 99071-95-1P 102936-57-2P 112380-21-9P 112380-22-0P  
 126125-54-0P 156589-82-1P 300830-79-9P 300830-80-2P  
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 300831-73-6P 300831-74-7P 300831-75-8P 300831-76-9P  
 300831-77-0P 300831-78-1P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP  
 (Preparation); RACT (Reactant or reagent)

(preparation of macrocyclic peptides active against the  
 hepatitis C virus)

## INDEX TERM:

300831-11-2P

ROLE: SPN (Synthetic preparation); PREP (Preparation)

(preparation of macrocyclic peptides active against the  
 hepatitis C virus)

## INDEX TERM:

768-94-5, Amantadine 36791-04-5, Ribavirin 42613-29-6,  
 Helicase 81669-70-7, Metalloprotease

ROLE: THU (Therapeutic use); BIOL (Biological study); USES  
(Uses)  
(preparation of macrocyclic peptides active against the  
hepatitis C virus)

INDEX TERM: 581980-39-4  
ROLE: PRP (Properties)  
(unclaimed protein sequence; preparation of macrocyclic  
peptides active against the hepatitis C virus)

INDEX TERM: 154485-12-8 242478-20-2 259221-97-1  
ROLE: PRP (Properties)  
(unclaimed sequence; preparation of macrocyclic peptides  
active against the hepatitis C virus)

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS  
RECORD.

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- (16) Anon; WO 9907733 1999 HCAPLUS
- (17) Anon; WO 9907734 1999 HCAPLUS
- (18) Anon; WO 9938888 1999 HCAPLUS
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Anon	1998			WO 9817679	HCAPLUS
Anon	1998			WO 9822496	HCAPLUS
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Anon	1998			WO 9853814 A1	HCAPLUS
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Anon	1999			WO 9907733 A2	HCAPLUS
Anon	1999			WO 9907733	HCAPLUS
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Anon	1999			WO 9964442	HCAPLUS
Anon	2000			WO 0009543 A2	HCAPLUS
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Llinas-Brunet	1998	8	1713	Bioorganic & Med Che	HCAPLUS
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Llinas-Brunet, M	2002			US Patent Applicatio	
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Seiyaku	1993			US 5192746 A	HCAPLUS

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L41 ANSWER 15 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:184286 HCAPLUS

ENTRY DATE: Entered STN: 11 Mar 2003

TITLE: Discovery of **BILN 2061**: A small-molecule inhibitor of the hepatitis C virus serine protease

AUTHOR(S): Llinas-Brunet, Montse; Bailey, Murray; Bolger, Gordon; Cameron, Dale; Cartier, Mireille; Faucher, Anne-Marie; Goudreau, Nathalie; Kukolj, George; Lagace, Lisette; Pause, Amim; Rancourt, Jean; Thibeault, Diane; Tsantrizos, Youla; Lamarre, Daniel

CORPORATE SOURCE: Research and Development, Boehringer Ingelheim (Canada) Ltd, Laval (Quebec), QC, H7S 2G5, Can.

SOURCE: Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-320. American Chemical Society: Washington, D. C.

CODEN: 69DSA4

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

ABSTRACT:

The inadequate efficacy and tolerability of current therapies for the infectious liver disease caused by Hepatitis C Virus have warranted significant efforts in the development of new therapeutics. Optimization studies on peptide inhibitors based on N-terminal cleavage products led to the discovery of **BILN 2061**, a small, selective and potent inhibitor of the NS3 serine protease. A distinguishing feature of **BILN**

\*\*\*2061\*\*\* is the presence of a C-terminal carboxylic acid functionality which provides exquisite selectivity with respect to other proteases.

\*\*\*BILN\*\*\* **2061** showed low nanomolar inhibition of HCV RNA replication using the replicon cell model system. **BILN 2061**

is orally bioavailable in various animal species. In view of the potent activity in vitro, good PK data in animal models and adequate pre-clin. safety profile, **BILN 2061** was selected for in-depth clin. evaluation in man as a novel antiviral compound for the treatment of HCV infection.

L41 ANSWER 16 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:886572 HCAPLUS

DOCUMENT NUMBER: 140:122161

ENTRY DATE: Entered STN: 12 Nov 2003

TITLE: An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus

AUTHOR(S): Lamarre, Daniel; Anderson, Paul C.; Bailey, Murray; Beaulieu, Pierre; Bolger, Gordon; Bonneau, Pierre; Boes, Michael; Cameron, Dale R.; Cartier, Mireille; Cordingley, Michael G.; Faucher, Anne-Marie; Goudreau, Nathalie; Kawai, Stephen H.; Kukolj, George; Lagace, Lisette; LaPlante, Steven R.; Narjes, Hans; Poupart, Marc-Andre; Rancourt, Jean; Sentjens, Roel E.; St. George, Roger; Simoneau, Bruno; Steinmann, Gerhard; Thibeault, Diane; Tsantrizos, Youla S.; Weldon, Steven M.; Yong, Chan-Loi; Llinas-Brunet, Montse

CORPORATE SOURCE: Departments of Biological Sciences, Boehringer Ingelheim (Canada) Ltd, Laval, QC, H7S 2G5, Can.

SOURCE: Nature (London, United Kingdom) (2003), 426(6963),  
186-189  
CODEN: NATUAS; ISSN: 0028-0836  
PUBLISHER: Nature Publishing Group  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
CLASSIFICATION: 1-5 (Pharmacology)  
ABSTRACT:

Hepatitis C virus (HCV) infection is a serious cause of chronic liver disease worldwide with more than 170 million infected individuals at risk of developing significant morbidity and mortality. Current interferon-based therapies are suboptimal especially in patients infected with HCV genotype 1, and they are poorly tolerated, highlighting the unmet medical need for new therapeutics. The HCV-encoded NS3 protease is essential for viral replication and has long been considered an attractive target for therapeutic intervention in HCV-infected patients. Here we identify a class of specific and potent NS3 protease inhibitors and report the evaluation of **BILN 2061**, a small mol. inhibitor biol. available through oral ingestion and the first of its class in human trials. Administration of **BILN 2061** to patients infected with HCV genotype 1 for 2 days resulted in an impressive reduction of HCV RNA plasma levels, and established proof-of-concept in humans for an HCV NS3 protease inhibitor. Our results further illustrate the potential of the viral-enzyme-targeted drug discovery approach for the development of new HCV therapeutics.

SUPPL. TERM: NS3 protease inhibitor BILN2061 antiviral hepatitis C virus  
INDEX TERM: Antiviral agents  
Hepatitis C virus  
Human  
(NS3 protease inhibitor with antiviral effects in humans  
infected with hepatitis C virus)  
INDEX TERM: Viral RNA  
ROLE: BSU (Biological study, unclassified); BIOL (Biological  
study)  
(NS3 protease inhibitor with antiviral effects in humans  
infected with hepatitis C virus)  
INDEX TERM: 149885-80-3, NS3 protease  
ROLE: BSU (Biological study, unclassified); BIOL (Biological  
study)  
(NS3 protease inhibitor with antiviral effects in humans  
infected with hepatitis C virus)  
INDEX TERM: 300832-84-2, **BILN 2061**  
ROLE: DMA (Drug mechanism of action); PAC (Pharmacological  
activity); THU (Therapeutic use); BIOL (Biological study);  
USES (Uses)  
(NS3 protease inhibitor with antiviral effects in humans  
infected with hepatitis C virus)  
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS  
RECORD.  
REFERENCE(S): (1) Anon; Science 1989, V244, P359  
(2) Anon; Science 1989, V244, P362  
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Boehringer Ingelheim Ca	2001			US 6323180 B1	HCAPLUS
Boehringer Ingelheim Ca	2003			US 6608027 B1	HCAPLUS
Chander, G	2002	36	S135	Hepatology	
Di Bisceglie, A	2002	35	224	Hepatology	
Di Bisceglie, A	1998	351	351	Lancet	MEDLINE
Foy, E	2003	300	1145	Science	HCAPLUS
Goudreau, N				J Med Chem submitted	
Hinrichsen, H	2002	36	297A	Hepatology Abst 866	
Kolykhalov, A	2000	74	2046	J Virol	HCAPLUS
Laplante, S	2000	10	2271	Bioorg Med Chem Lett	HCAPLUS
Laplante, S	1999	274	18618	J Biol Chem	HCAPLUS
Llinas-Brunet, M	1998	8	1713	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	1998	8	2719	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	2000	10	2267	Bioorg Med Chem Lett	HCAPLUS
Lohmann, V	1999	285	103	Science	
Mercer, D	2001	7	927	Nature Med	HCAPLUS
Narjes, H	2002	36		Hepatology Abst 800	
Neumann, A	2000	182	28	J Infect Dis	MEDLINE
Neumann, A	1998	282	103	Science	HCAPLUS
Pause, A	2003	278	20374	J Biol Chem	HCAPLUS
Poupart, M	2001	66	4743	J Org Chem	HCAPLUS
Reed, K	2000	242	55	Curr Top Microbiol I	HCAPLUS
Schechter, I	1967	27	157	Biochem Biophys Res	HCAPLUS
Steinkuhler, C	1998	37	8899	Biochemistry	MEDLINE
Tan, S	2002	1	867	Nature Rev Drug Disc	HCAPLUS

Tsantrizos, Y	2003	42	1356	Angew Chem Int Edn E	HCAPLUS
Zeuzem, S	2001	120	1438	Gastroenterology	HCAPLUS

L41 ANSWER 17 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:725652 HCAPLUS

DOCUMENT NUMBER: 133:296659

ENTRY DATE: Entered STN: 13 Oct 2000

TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus

INVENTOR(S): Tsantrizos, Youla S.; Cameron, Dale R.; Faucher, Anne-marie; Ghio, Elise; Goudreau, Nathalie; Halmos, Teddy; Llinas-brunet, Montse

PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.

SOURCE: PCT Int. Appl., 154 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

INT. PATENT CLASSIF.:

MAIN: C07K005-08

SECONDARY: C07K005-078; A61K038-05; A61K038-06; A61P031-14

CLASSIFICATION: 34-3 (Amino Acids, Peptides, and Proteins)

Section cross-reference(s): 1, 15

FAMILY ACC. NUM. COUNT: 2

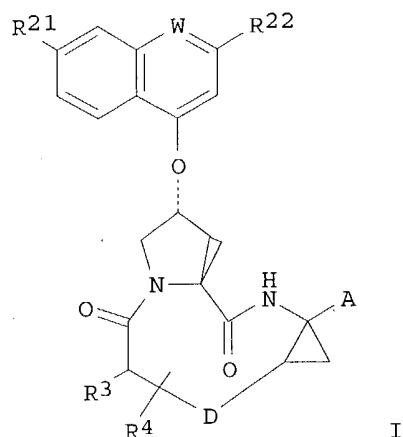
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059929	A1	20001012	WO 2000-CA353	20000403
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1169339	A1	20020109	EP 2000-913999	20000403
EP 1169339	B1	20040929		
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BR 2000009599	A	20020115	BR 2000-9599	20000403
TR 200102878	T2	20020121	TR 2001-200102878	20000403
EE 200100516	A	20021216	EE 2001-516	20000403
NZ 515286	A	20040227	NZ 2000-515286	20000403
EP 1437362	A1	20040714	EP 2004-9264	20000403
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BG 105970	A	20020531	BG 2001-105970	20011002
HR 2001000720	A1	20021231	HR 2001-720	20011004
NO 2001004857	A	20011031	NO 2001-4857	20011005
PRIORITY APPLN. INFO.:			US 1999-128011P	P 19990406
			EP 2000-913999	A3 20000403
			WO 2000-CA353	W 20000403

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000059929	ICM	C07K005-08
	ICS	C07K005-078; A61K038-05; A61K038-06; A61P031-14
OTHER SOURCE(S):		MARPAT 133:296659

## GRAPHIC IMAGE:



## ABSTRACT:

Macrocyclic peptides I [W = CH or N; R21 = H, halo, alkyl, cycloalkyl, haloalkyl, alkoxy, cycloalkoxy, hydroxy, or an amino group; R22 = H, halo, alkyl, cycloalkyl, haloalkyl, thioalkyl, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkyl, aryl or heteroaryl; R3 = hydroxy, NH2, aryl- or heteroaryl-amino, NHCOR32, CONHR32, CO2R32, where R32 is alkyl or cycloalkyl; D is a 5 to 10-atom saturated or unsatd. alkylene chain optionally containing one to three heteroatoms independently selected from: O, S, or NH or substituted imino; R4 = H or from one to three substituents at any carbon atom of chain D; A is an amide or carboxylic acid group or a pharmaceutically acceptable salt or ester; two diastereomers may exist at the cyclopropane moiety] were prepared which are active in-vitro and in cellular assays against the NS3 protease of the hepatitis C virus. Thus, macrocyclic peptide I [W = N; R21, R22, R4 = H; A = CO2H; R3CH-D = (S)-(Me3CO2CNH)CH(CH2)3CH:CH(CH2)2-E (syn to acid)] was prepared and showed IC50 > 0.1 μM in the full-length NS3-NS4A heterodimer protein fluorogenic assay.

SUPPL. TERM: cyclic peptide prepn hepatitis C virus inhibitor  
 INDEX TERM: Hepatitis C virus  
 Immunomodulators  
 (preparation of macrocyclic peptides active against the hepatitis C virus)  
 INDEX TERM: Macrocyclic compounds  
 Peptides, preparation  
 ROLE: BAC (Biological activity or effector, except adverse);  
 BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of macrocyclic peptides active against the hepatitis C virus)  
 INDEX TERM: Interferons  
 ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (preparation of macrocyclic peptides active against the hepatitis C virus)  
 INDEX TERM: 300831-32-7P 300831-33-8P 300831-34-9P 300831-79-2P  
 300831-80-5P 300831-81-6P 300831-82-7P 300831-83-8P  
 300831-84-9P 300831-85-0P 300831-86-1P 300831-87-2P

300831-88-3P	300831-89-4P	300831-90-7P	300831-91-8P
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301188-00-1P			

ROLE: BAC (Biological activity or effector, except adverse);  
 BSU (Biological study, unclassified); SPN (Synthetic  
 preparation); THU (Therapeutic use); BIOL (Biological  
 study); PREP (Preparation); USES (Uses)

(preparation of macrocyclic peptides active against the  
 hepatitis C virus)

## INDEX TERM:

37259-58-8, Serine protease

ROLE: BPR (Biological process); BSU (Biological study,  
 unclassified); BIOL (Biological study); PROC (Process)

(preparation of macrocyclic peptides active against the  
 hepatitis C virus)

## INDEX TERM:

62-56-6, Thiourea, reactions 78-39-7, Triethyl  
 orthoacetate 79-22-1, Methyl chloroformate 105-56-6,  
 Ethyl cyanoacetate 288-13-1, Pyrazole 288-32-4,  
 Imidazole, reactions 536-90-3, m-Anisidine 541-16-2,  
 Di-tert-butyl malonate 543-27-1, Isobutyl chloroformate  
 563-80-4, 3-Methyl-2-butanone 591-08-2, n-Acetylthiourea  
 598-52-7, n-Methylthiourea 625-53-6, n-Ethylthiourea  
 696-59-3, 2,5-Dimethoxytetrahydrofuran 822-36-6,  
 4-Methylimidazole 934-60-1, 6-Methylpicolinic acid  
 1068-90-2, Diethyl acetamidomalonate 1113-41-3,  
 L-Penicillamine 1113-59-3, 3-Bromopyruvic acid  
 1119-51-3, 4-Pentenyl bromide 1719-76-2, Isopropylthiourea  
 2385-77-5 2592-18-9 2695-48-9, 8-Bromo-1-octene  
 3282-30-2, Pivaloyl chloride 4285-48-7 7554-65-6,  
 4-Methylpyrazole 10387-40-3, Potassium thioacetate  
 13726-85-7 16982-21-1, Ethyl thiooxamate 22059-22-9,  
 Acetamidoxime 29681-39-8 50413-30-4 50715-28-1  
 82121-05-9, 4-Hydroxy-7-methoxyquinoline 85866-02-0,  
 7-Octene-1,2-diol 90719-32-7 102195-79-9 113240-46-3,

Malonic acid monoallyl ester 126690-67-3 204711-97-7  
 259214-64-7 259214-73-8 300831-45-2 300831-47-4  
 300831-50-9 300831-58-7 300831-62-3 300831-65-6  
 300831-67-8

ROLE: RCT (Reactant); RACT (Reactant or reagent)  
 (preparation of macrocyclic peptides active against the  
 hepatitis C virus)

## INDEX TERM:

616-47-7P, 1-Methylimidazole 3350-20-7P 17206-61-0P,  
 6-Heptenal 19967-55-6P 20485-43-2P 27191-09-9P,  
 m-Anisidine hydrochloride 29082-92-6P 31642-67-8P,  
 8-Nonenoic acid 42465-53-2P 55327-87-2P,  
 Acetamidomalonic acid 72086-72-7P 79479-07-5P  
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ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP  
 (Preparation); RACT (Reactant or reagent)  
 (preparation of macrocyclic peptides active against the  
 hepatitis C virus)

## INDEX TERM:

300831-11-2P

ROLE: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of macrocyclic peptides active against the  
 hepatitis C virus)

## INDEX TERM:

768-94-5, Amantadine 36791-04-5, Ribavirin 42613-29-6,  
 Helicase 81669-70-7, Metalloprotease  
 ROLE: THU (Therapeutic use); BIOL (Biological study); USES  
 (Uses)

(preparation of macrocyclic peptides active against the  
 hepatitis C virus)

## REFERENCE COUNT:

1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD.

## REFERENCE(S):

(1) Boehringer Ingelheim Ca Ltd; WO 9907733 A 1999 HCAPLUS

## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Boehringer Ingelheim Ca	1999			WO 9907733 A	HCAPLUS

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L41 ANSWER 18 OF 36 MEDLINE on STN  
 ACCESSION NUMBER: 2004098430 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 14988742  
 TITLE: Gateways to clinical trials.  
 AUTHOR: Bayes M; Rabasseda X; Prous J R  
 CORPORATE SOURCE: Prous Science, PO Box 540, 08080 Barcelona, Spain..  
 mbayes@prous.com  
 SOURCE: Methods and findings in experimental and clinical  
 pharmacology, (2004 Jan-Feb) 26 (1) 53-84. Ref: 200  
 Journal code: 7909595. ISSN: 0379-0355.  
 PUB. COUNTRY: Spain  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW LITERATURE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200405  
 ENTRY DATE: Entered STN: 20040302  
 Last Updated on STN: 20040510  
 Entered Medline: 20040507

AB Gateways to Clinical Trials is a guide to the most recent clinical trials in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies Knowledge Area of Prous Science Integrity, the drug discovery and development portal, <http://integrity.prous.com>. This issue focuses on the following selection of drugs: Abetimus sodium, Ad5-FGF4, adeno-Interferon gamma, AE-941, AERx, alemtuzumab, alicaforsen sodium, almotriptan, alpharadin, anakinra, anatumomab mafenatox, ANG-453, anti-CTLA-4 Mab, AP-12009, aprepitant, aripiprazole, arsenic trioxide, astemizole, atlizumab, atomoxetine hydrochloride; Bevacizumab, BG-9928, BMS-188667, botulinum toxin type B, BufferGel; Caffeine, CDP-870, cetuximab, cilomilast, **ciluprevir**, clofarabine, continuous erythropoiesis receptor activator, CP-461; Darbepoetin alfa, deferasirox, desloratadine, desoxyepothilone B, diflomotecan, dolasetron, drotrecogin alfa (activated), duloxetine hydrochloride; ED-71, efalizumab, efaproxiral sodium, EKB-569, eletriptan, EMD-72000, enfuvirtide, erlotinib hydrochloride, escitalopram oxalate, etoricoxib; Fampridine, ferumoxytol, fondaparinux sodium; Gadofosveset sodium, gastrazole, gefitinib, gemtuzumab ozogamicin, gepirone hydrochloride glutamine; hLM609, HSPPC-96, human insulin; IDD-1, imatinib mesylate, indisulam, inhaled insulin, ixabepilone; Keratinocyte growth factor; Lapatinib, laquinimod, LDP-02, LE-SN38, levetiracetam, levosimendan, licofelone, liposomal doxorubicin, liposomal NDDP, lopinavir, lumiracoxib, LY-156735; **Morphine** hydrochloride, **morphine**-6-glucuronide, motexafin gadolinium, MS-27-275, MVA-5T4, MVA-Muc1-IL-2; Nemifitide ditriflutate, neridronic acid nitronaproxen, NSC-683864, NSC-703940, NVP-LAF-237; Oblimersen sodium, ocinaplon, oncomyc-NG, OPC-28326, ortataxel, ospemifene; Palonosetron hydrochloride, PEG-filgrastim peginterferon alfa-2(a), peginterferon alfa-2b, pegsunercept, pemetrexed disodium, pregabalin, prilocaine, pyridoxamine; RDP-58, recombinant glucagon-like peptide-1 (7-36) amide, recombinant human ApoA-I milano/phospholipid complex; SB-715992, soblidotin, sodium dichloroacetate, St. John's Wort extract; TAS-102, terfenadine, TG-1024, TG-5001, 4'-Thio-ara-C, tipranavir, topixantrone hydrochloride, trabectedin, transdermal selegiline, trimethoprim, troxacitabine, TT-232; Vatalanib succinate, vinflunine; Ximelagatran; Ziprasidone hydrochloride, Zoledronic acid monohydrate.

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AB Gateways to Clinical Trials is a guide to the most recent clinical trials

in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies Knowledge Area of Prous Science Integrity, the drug discovery and development portal, <http://integrity.prous.com>. This issue focuses on the following selection of drugs: Abetimus sodium, Ad5-FGF4, adeno-Interferon gamma, AE-941, AERx, alemtuzumab, alicaforsen sodium, almotriptan, alpharadin, anakinra, anatumomab mafenatox, ANG-453, anti-CTLA-4 Mab, AP-12009, aprepitant, aripiprazole, arsenic trioxide, astemizole, atlizumab, atomoxetine hydrochloride; Bevacizumab, BG-9928, BMS-188667, botulinum toxin type B, BufferGel; Caffeine, CDP-870, cetuximab, cilomilast, **ciluprevir**, clofarabine, continuous erythropoiesis receptor activator, CP-461; Darbepoetin alfa, deferasirox, desloratadine, desoxyepothilone B, diflomotecan, dolasetron, drotrecogin alfa (activated), duloxetine hydrochloride; ED-71, efalizumab, efaproxiral sodium, EKB-569, eletriptan, EMD-72000, enfuvirtide, erlotinib hydrochloride, escitalopram oxalate, etoricoxib; Fampridine, ferumoxytol, fondaparinux sodium; Gadofosveset sodium, gastrazole, gefitinib, gemtuzumab ozogamicin, gepirone hydrochloride glutamine; hLM609, HSPPC-96, human insulin; IDD-1, imatinib mesylate, indisulam, inhaled insulin, ixabepilone; Keratinocyte growth factor; Lapatinib, laquinimod, LDP-02, LE-SN38, levetiracetam, levosimendan, licofelone, liposomal doxorubicin, liposomal NDDP, lopinavir, lumiracoxib, LY-156735; **Morphine** hydrochloride, **morphine**-6-glucuronide, motexafin gadolinium, MS-27-275, MVA-5T4, MVA-Muc1-IL-2; Nemifitide ditriflutate, neridronic acid nitronaproxen, NSC-683864, NSC-703940, NVP-LAF-237; Oblimersen sodium, ocinaplon, oncomyc-NG, OPC-28326, ortataxel, ospemifene; Palonosetron hydrochloride, PEG-filgrastim peginterferon alfa-2(a), peginterferon alfa-2b, pegsunercept, pemetrexed disodium, pregabalin, prilocaine, pyridoxamine; RDP-58, recombinant glucagon-like peptide-1 (7-36) amide, recombinant human ApoA-I milano/phospholipid complex; SB-715992, soblidotin, sodium dichloroacetate, St. John's Wort extract; TAS-102, terfenadine, TG-1024, TG-5001, 4'-Thio-ara-C, tipranavir, topixantrone hydrochloride, trabectedin, transdermal selegiline, trimethoprim, troxacitabine, TT-232; Vatalanib succinate, vinflunine; Ximelagatran; Ziprasidone hydrochloride, Zoledronic acid monohydrate.

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L41 ANSWER 19 OF 36 MEDLINE on STN  
 ACCESSION NUMBER: 2004035206 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 14735233  
 TITLE: Gateways to clinical trials.  
 AUTHOR: Bayes M; Rabasseda X; Prous J R  
 CORPORATE SOURCE: Prous Science, Barcelona, Spain.. mbayes@prous.com  
 SOURCE: Methods and findings in experimental and clinical pharmacology, (2003 Dec) 25 (10) 831-55.  
 Journal code: 7909595. ISSN: 0379-0355.  
 PUB. COUNTRY: Spain  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200404  
 ENTRY DATE: Entered STN: 20040122  
 Last Updated on STN: 20040501  
 Entered Medline: 20040430

AB Gateways to Clinical Trials is a guide to the most recent clinical trials in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies Knowledge Area of Prous Science Integrity, the drug discovery and development portal, <http://integrity.prous.com>. This issue focuses on the following selection of drugs: Abetimus sodium, adalimumab, alefacept, alemtuzumab,

almotriptan, AMGN-0007, anakinra, anti-CTLA-4 Mab, L-arginine hydrochloride, arzoxifene hydrochloride, astemizole, atazanavir sulfate, atlizumab; Belimumab, BG-9928, binodenoson, bosentan, botulinum toxin type B, bovine lactoferrin, BufferGel; Caspofungin acetate, ciclesonide, cilomilast, **ciluprevir**, clofarabine, CVT-3146; Darbepoetin alfa, desloratadine, diflomotecan, doripenem, dronedarone hydrochloride, drotrecogin alfa (activated), DT388-GM-CSF, duloxetine hydrochloride, E-5564, efalizumab, enfuvirtide, esomeprazole magnesium, estradiol acetate, ETC-642, exenatide, exisulind, ezetimib; Febuxostat; Gallium maltolate, ganirelix acetate, garenoxacin mesilate, gefitinib; H11, HuMax; IL-15, IDD-1, IGIV-C, imatinib mesylate, ISIS-14803, ITF-1697, ivabradine hydrochloride; KRN-5500; L-365260, levetiracetam, levosimendan, licofelone, linezolid, LJP-1082, lopinavir lumiracoxib; MCC-478, melatonin, **morphine** hydrochloride, **morphine** -6-glucuronide, moxidectin; N-Acetylcarnosine, natalizumab, NM-702, NNC-05-1869, NSC-703940; Ocina-plon OM-89, omalizumab, omeprazole/ sodium bicarbonate, OPC-28326, ospemifene; PEG-filgrastim peginterferon alfa-2a, pegsunercept, pirfenidone, pralmorelin, pregabalin; Recombinant glucagon-like peptide-1 (7-36) amide, repifermin, RSD-1235; S-8184, selodenoson, sodium dichloroacetate, suberanilohydroxamic acid; TAS-102, terfenadine, teriparatide, tipranavir troxacetabine; Ximelagatran; YM-337.  
(c) 2003 Prous Science

AB Gateways to Clinical Trials is a guide to the most recent clinical trials in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies Knowledge Area of Prous Science Integrity, the drug discovery and development portal, <http://integrity.prous.com>. This issue focuses on the following selection of drugs: Abetimus sodium, adalimumab, alefacept, alemtuzumab, almotriptan, AMGN-0007, anakinra, anti-CTLA-4 Mab, L-arginine hydrochloride, arzoxifene hydrochloride, astemizole, atazanavir sulfate, atlizumab; Belimumab, BG-9928, binodenoson, bosentan, botulinum toxin type B, bovine lactoferrin, BufferGel; Caspofungin acetate, ciclesonide, cilomilast, **ciluprevir**, clofarabine, CVT-3146; Darbepoetin alfa, desloratadine, diflomotecan, doripenem, dronedarone hydrochloride, drotrecogin alfa (activated), DT388-GM-CSF, duloxetine hydrochloride, E-5564, efalizumab, enfuvirtide, esomeprazole magnesium, estradiol acetate, ETC-642, exenatide, exisulind, ezetimib; Febuxostat; Gallium maltolate, ganirelix acetate, garenoxacin mesilate, gefitinib; H11, HuMax; IL-15, IDD-1, IGIV-C, imatinib mesylate, ISIS-14803, ITF-1697, ivabradine hydrochloride; KRN-5500; L-365260, levetiracetam, levosimendan, licofelone, linezolid, LJP-1082, lopinavir lumiracoxib; MCC-478, melatonin, **morphine** hydrochloride, **morphine** -6-glucuronide, moxidectin; N-Acetylcarnosine, natalizumab, NM-702, NNC-05-1869, NSC-703940; Ocina-plon OM-89, omalizumab, omeprazole/ sodium bicarbonate, OPC-28326, ospemifene; PEG-filgrastim peginterferon alfa-2a, pegsunercept, pirfenidone, pralmorelin, pregabalin; Recombinant glucagon-like peptide-1 (7-36) amide, repifermin, RSD-1235; S-8184, selodenoson, sodium dichloroacetate, suberanilohydroxamic acid; TAS-102, terfenadine, teriparatide, tipranavir troxacetabine; Ximelagatran; YM-337.  
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L41 ANSWER 20 OF 36 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:133738 BIOSIS

DOCUMENT NUMBER: PREV200400132108

TITLE: VX-950, a HCV protease inhibitor, retains potency against BILN-2061 resistant replicon cells.

AUTHOR(S): Lin, Chao [Reprint Author]; Lin, Kai [Reprint Author]; Gates, Cynthia A. [Reprint Author]; Ma, Sue [Reprint Author]; Brennan, Debra [Reprint Author]; Fulghum, John

[Reprint Author]; Hsiao, Hsun-Mei [Reprint Author]; Rao, Govinda [Reprint Author]; Wei, Yunyi [Reprint Author]; Alford, John [Reprint Author]; Perni, Robert B. [Reprint Author]; Kwong, Ann D. [Reprint Author]

CORPORATE SOURCE: Vertex Pharmaceuticals Inc., Cambridge, MA, USA  
SOURCE: Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp. 638A. print.  
Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, USA. October 24-28, 2003. American Association for the Study of Liver Diseases.  
ISSN: 0270-9139 (ISSN print).

DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 10 Mar 2004  
Last Updated on STN: 10 Mar 2004

AB Due to the limited efficacy of current therapies for chronic Hepatitis C virus (HCV) infected patients, more specific and potent anti-HCV drugs are needed. We have been developing small molecule inhibitors of the HCV NS3cndot4A protease using a **structure**-based, rational drug design process. We recently selected VX-950 as a candidate for clinical development. In this report, we describe resistance studies, using an in vitro replicon system, conducted on VX-950 and **BILN-2061**, another HCV protease inhibitor, which was recently reported to be in clinical trials. Distinct drug-resistant mutations were identified for both protease inhibitors. Mutants that are resistant to **BILN-2061** remain fully sensitive to VX-950. Characterization of enzymatic, kinetic, and anti-viral properties will be presented for mutations that confer resistance to VX-950 or to **BILN-2061**.

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L41 ANSWER 21 OF 36 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:123506 BIOSIS  
DOCUMENT NUMBER: PREV200400116725  
TITLE: Sensitivity of NS3 serine proteases from various Hepatitis C Virus genotypes to the antiviral compound BILN 2061.  
AUTHOR(S): Thibeault, Diane [Reprint Author]; Bousquet, Christiane [Reprint Author]; Gingras, Rock [Reprint Author]; Lagace, Lisette [Reprint Author]; Maurice, Roger [Reprint Author]; White, Peter W. [Reprint Author]; Lamarre, Daniel [Reprint Author]  
CORPORATE SOURCE: Boehringer Ingelheim (Canada) Ltd, Laval, PQ, Canada  
SOURCE: Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp. 300A. print.

Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, USA. October 24-28, 2003. American Association for the Study of Liver Diseases.

ISSN: 0270-9139 (ISSN print).

DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 3 Mar 2004

Last Updated on STN: 3 Mar 2004

AB Introduction: Genetic heterogeneity is an important feature of Hepatitis C Virus (HCV) genomes with six known genotypes and more than 50 subtypes. Genotypes 1, 2 and 3 are broadly distributed in patients around the world, whereas the other types are more geographically restricted. The peptidomimetic inhibitor **BILN 2061**, optimized to have a high affinity for genotype 1 NS3 protease, has been reported to reduce viral load in genotype 1 HCV infected individuals. In this study, the ability of **BILN 2061** to inhibit the NS3 proteases from the other widespread genotypes 2 and 3 was assessed. Methods: The NS3 protease domains and the NS3-NS4A proteins of genotypes 1a, 1b, 2ac, 2b and 3a were cloned, expressed in *E. coli* and purified. Protease activity was evaluated using fluorogenic decapeptide substrates derived from the amino acid sequence at the NS4A-NS4B and NS5A-NS5B junctions. Results: The activity of the NS3 protease domains revealed no major differences among the various genotypes. For the NS3-NS4A proteins, the catalytic efficiencies of the non-genotype 1 enzymes, although higher than the ones observed for the corresponding protease domains, were similar to that observed for genotype 1 (within 3-fold). Differences in activity observed among genotypes were mainly related to changes in *k<sub>cat</sub>* values. Binding constant (*K<sub>i</sub>*) values for **BILN 2061** were similar among non-genotype 1 proteases with *K<sub>i</sub>*'s ranging from 80-90 nM for the NS3-NS4A proteins, up to a 60-fold reduction in affinity when compared to genotype 1. Conclusion: The major pharmacophores of **BILN 2061** were optimized for binding to HCV genotype 1 NS3 protease. Thus binding of **BILN 2061** was found to be more sensitive to naturally occurring polymorphism of the protease than the unnatural surrogate substrates used in this study. Even though a decreased sensitivity of non-genotype 1 proteases to **BILN 2061** was observed, **BILN 2061** remains a potent inhibitor of the NS3-NS4A protein with *K<sub>i</sub>* values below 100 nM. The *in vitro* potency in conjunction with the good pharmacokinetics data reported in man suggests that **BILN 2061** may demonstrate antiviral activity in non-genotype 1 HCV infected individuals.

AB Introduction: Genetic heterogeneity is an important feature of Hepatitis C Virus (HCV) genomes with six known genotypes and more than 50 subtypes. Genotypes 1, 2 and 3 are broadly distributed in patients around the world, whereas the other types are more geographically restricted. The peptidomimetic inhibitor **BILN 2061**, optimized to have a high affinity for genotype 1 NS3 protease, has been reported to reduce viral load in genotype 1 HCV infected individuals. In this study, the ability of **BILN 2061** to inhibit the NS3 proteases from the other widespread genotypes 2 and 3 was assessed. Methods: The NS3 protease domains and the NS3-NS4A proteins of genotypes 1a, 1b, 2ac, 2b and 3a were cloned, expressed in *E. coli* and purified. Protease activity was evaluated using fluorogenic decapeptide substrates derived from the amino acid sequence at the NS4A-NS4B and NS5A-NS5B junctions. Results: The activity of the NS3 protease domains revealed no major differences among the various genotypes. For the NS3-NS4A proteins, the catalytic efficiencies of the non-genotype 1 enzymes, although higher than the ones

observed for the corresponding protease domains, were similar to that observed for genotype 1 (within 3-fold). Differences in activity observed among genotypes were mainly related to changes in kcat values. Binding constant (Ki) values for **BILN 2061** were similar among non-genotype 1 proteases with Ki's ranging from 80-90 nM for the NS3-NS4A proteins, up to a 60-fold reduction in affinity when compared to genotype 1. Conclusion: The major pharmacophores of **BILN 2061** were optimized for binding to HCV genotype 1 NS3 protease. Thus binding of **BILN 2061** was found to be more sensitive to naturally occurring **polymorphism** of the protease than the unnatural surrogate substrates used in this study. Even though a decreased sensitivity of non-genotype 1 proteases to **BILN 2061** was observed, **BILN 2061** remains a potent inhibitor of the NS3-NS4A protein with Ki values below 100 nM. The in vitro potency in conjunction with the good pharmacokinetics data reported in man suggests that **BILN 2061** may demonstrate antiviral activity in non-genotype 1 HCV infected individuals.

L41 ANSWER 22 OF 36 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:123273 BIOSIS

DOCUMENT NUMBER: PREV200400116587

TITLE: VX-950: A tight-binding HCV protease inhibitor with a superior sustained inhibitory response in HCV replicon cells.

AUTHOR(S): Lin, Kai [Reprint Author]; Gates, Cynthia A. [Reprint Author]; Luong, Yu-Ping [Reprint Author]; Perni, Robert B. [Reprint Author]; Kwong, Ann D. [Reprint Author]

CORPORATE SOURCE: Vertex Pharmaceuticals Inc, Cambridge, MA, USA

SOURCE: Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp. 222A. print.

Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, USA. October 24-28, 2003. American Association for the Study of Liver Diseases.

ISSN: 0270-9139 (ISSN print).

DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 3 Mar 2004

Last Updated on STN: 3 Mar 2004

AB We have been developing HCV NS3cndot4A protease inhibitors using a **structure**-based, rational drug design process. In these studies, we compared our clinical candidate, VX-950, to **BILN-2061**, another HCV protease inhibitor in clinical development (2002 AASLD Mtg). VX-950 and **BILN-2061** exhibit inhibition mechanisms that appear kinetically distinct from each another. Additional studies were designed to investigate the effects of these different mechanisms of protease inhibition on replication in a replicon system. HCV replicon cells were incubated with concentrations of VX-950 or **BILN-2061** that were fixed multiples (X10 and X50) of their respective IC50's in the absence of G418. Two days after the addition of compound, the rate of inhibition of HCV replicon RNA was similar for both drugs. In contrast, at late times (12-15 days) after the addition of drug, VX-950 suppressed HCV replicon RNA to dramatically lower levels than **BILN-2061** (typically 1-2 log10). When the same experiment was performed in the presence of G418, more colonies of resistant cells grew in the cultures containing **BILN-2061** than VX-950. These results indicate that VX-950 has a more potent and sustainable antiviral response in HCV replicon cells than **BILN-2061**.

. These findings will be discussed, in the context of the different chemical **structures** and enzyme inhibition mechanisms of these two inhibitors.

AB We have been developing HCV NS3cndot4A protease inhibitors using a **structure**-based, rational drug design process. In these studies, we compared our clinical candidate, VX-950, to **BILN-2061**, another HCV protease inhibitor in clinical development (2002 AASLD Mtg). VX-950 and **BILN-2061** exhibit inhibition mechanisms that appear kinetically distinct from each another. Additional studies were designed to investigate the effects of these different mechanisms of protease inhibition on replication in a replicon system. HCV replicon cells were incubated with concentrations of VX-950 or **BILN-2061** that were fixed multiples (X10 and X50) of their respective IC50's in the absence of G418. Two days after the addition of compound, the rate of inhibition of HCV replicon RNA was similar for both drugs. In contrast, at late times (12-15 days) after the addition of drug, VX-950 suppressed HCV replicon RNA to dramatically lower levels than **BILN-2061** (typically 1-2 log10). When the same experiment was performed in the presence of G418, more colonies of resistant cells grew in the cultures containing **BILN-2061** than VX-950. These results indicate that VX-950 has a more potent and sustainable antiviral response in HCV replicon cells than **BILN-2061**.  
. These findings will be discussed, in the context of the different chemical **structures** and enzyme inhibition mechanisms of these two inhibitors.

=>

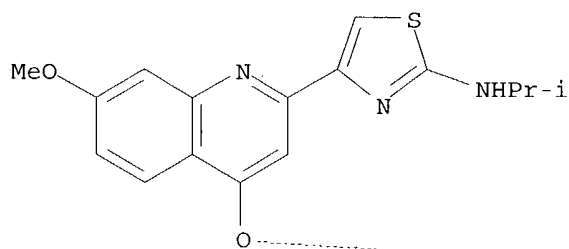
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L41 ANSWER 23 OF 36 ADISINSIGHT COPYRIGHT (C) 2004 Adis Data Information BV  
on STN

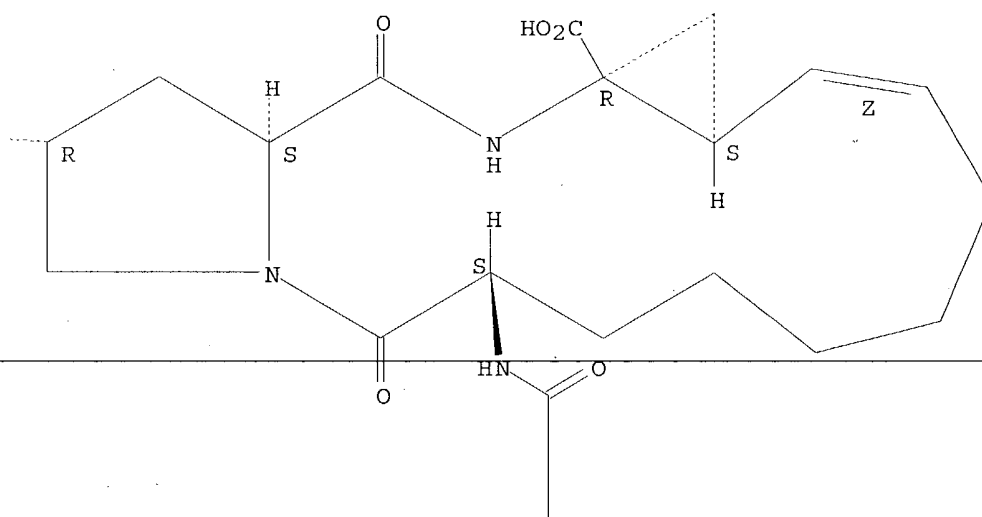
ACCESSION NUMBER: 2002:466 ADISINSIGHT  
SOURCE: Adis R&D Insight  
DOCUMENT NO: 017325  
CHANGE DATE: Jun 1, 2004  
GENERIC NAME: Ciluprevir  
SYNONYM: **BILN 2061; BILN 2061 ZW; BILN-2061**  
CHEMICAL NAME: Cyclopropa(e)pyrrolo(1,2-a)(1,4)diazacyclopentadecine-14a(5H)-carboxylic acid, 6-(((cyclopentyloxy)carbonyl)amino)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-((7-methoxy-2-(2-((1-methylethyl)amino)-4-thiazolyl)-4-quinolinyl)oxy)-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)-  
MOLECULAR FORMULA: C40 H50 N6 O8 S  
CAS REGISTRY NO.: 300832-84-2  
STRUCTURE:

Absolute stereochemistry.  
Double bond geometry as shown.

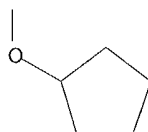
PAGE 1-A



PAGE 1-B



PAGE 2-B



EPHMA ATC CODE:  
WHO ATC CODE:  
HIGHEST DEV. PHASE:

J5B Antivirals, excluding anti-HIV products  
J05A-E Protease inhibitors  
Suspended II

COMPANY INFORMATION  
ORIGINATOR:

Boehringer Ingelheim (Canada); Boehringer Ingelheim

PARENT: Pharma KG (Germany)  
Boehringer Ingelheim

WORD COUNT: 711

L41 ANSWER 24 OF 36 ADISINSIGHT COPYRIGHT (C) 2004 Adis Data Information BV  
on STN

ACCESSION NUMBER: 2000:1398 ADISINSIGHT  
SOURCE: Adis R&D Insight  
DOCUMENT NO: 014557  
CHANGE DATE: Dec 23, 2003  
GENERIC NAME: Research programme: hepatitis C virus NS3 protease  
inhibitors -Boehringer Ingelheim  
SYNONYM: Hepatitis C virus NS3 protease inhibitors research  
programme -Boehringer Ingelheim

MOLECULAR FORMULA:Unspecified

STRUCTURE:

STRUCTURE DIAGRAM IS NOT AVAILABLE

EPHMRA ATC CODE: J5B Antivirals, excluding anti-HIV products  
WHO ATC CODE: J05A-E Protease inhibitors  
HIGHEST DEV. PHASE: Preclinical

COMPANY INFORMATION

ORIGINATOR: Boehringer Ingelheim (Canada); Boehringer Ingelheim  
(Germany)

PARENT: Boehringer Ingelheim

WORD COUNT: 365

L41 ANSWER 25 OF 36 ADISINSIGHT COPYRIGHT (C) 2004 Adis Data Information BV  
on STN

ACCESSION NUMBER: 1998:10260 ADISINSIGHT  
SOURCE: Adis R&D Insight  
DOCUMENT NO: 011269  
CHANGE DATE: Sep 16, 2004  
GENERIC NAME: VX 950  
SYNONYM: Hepatitis C virus protease inhibitors research programme  
- Vertex/Eli Lilly; LY 570310; LY-570310; LY570310

MOLECULAR FORMULA:Unspecified

STRUCTURE:

STRUCTURE DIAGRAM IS NOT AVAILABLE

EPHMRA ATC CODE: J5B Antivirals, excluding anti-HIV products  
WHO ATC CODE: J05A-E Protease inhibitors  
HIGHEST DEV. PHASE: Phase I

COMPANY INFORMATION

ORIGINATOR: Eli Lilly (United States); Vertex Pharmaceuticals  
(United States)

PARENT: Eli Lilly; Vertex Pharmaceuticals

OTHER SOURCES: 809035665; 809038928  
WORD COUNT: 1068

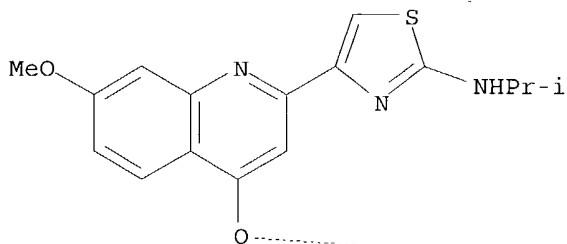
L41 ANSWER 26 OF 36 IMSRESEARCH COPYRIGHT 2004 IMSWORLD on STN

ACCESSION NUMBER: 2002:1036 IMSRESEARCH  
SOURCE: R&D Focus, (16 Feb 2004)  
GENERIC NAME: **ciluprevir; ciluprevir**

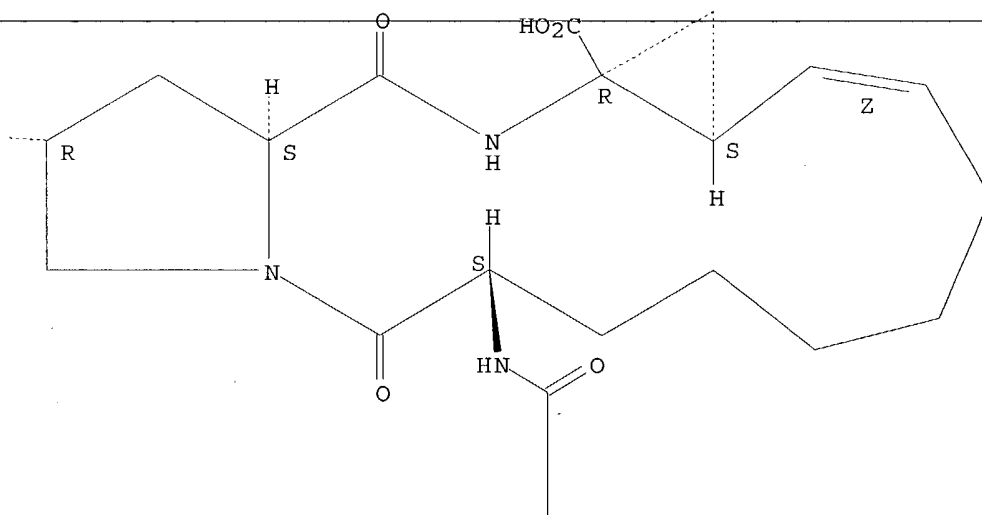
REFERENCE: pINN  
 LABORATORY NAME: BILN 2061; BILN 2061ZW  
 CHEMICAL NAME: (2R,6S,12Z,13aS,14aR,16aS)-6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid  
 CAS REGISTRY NO.: 300832-84-2  
 STRUCTURE:

Absolute stereochemistry.  
 Double bond geometry as shown.

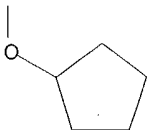
PAGE 1-A



PAGE 1-B



PAGE 2-B



DERIVATIVE(S): 300832-84-2ciluprevir  
 CLASSIFICATION: J5B Antivirals, Excluding Anti-HIV Products  
 HIGHEST DEV. PHASE: Phase II (40)

## COMPANY INFORMATION:

Type	Company	Nationality
Originator	Boehringer Ingelheim	Germany, Federal Republic of
Assignee	Boehringer Ingelheim	

L41 ANSWER 27 OF 36 IMSRESEARCH COPYRIGHT 2004 IMSWORLD on STN

ACCESSION NUMBER: 2002:50 IMSRESEARCH  
 SOURCE: R&D Focus, (21 Jun 2004)  
 LABORATORY NAME: VX 950; LY 570310  
 STRUCTURE:

STRUCTURE DIAGRAM IS NOT AVAILABLE

CLASSIFICATION: J5B Antivirals, Excluding Anti-HIV Products  
 HIGHEST DEV. PHASE: Phase I (30)

## COMPANY INFORMATION:

Type	Company	Nationality	Region
Originator	Vertex	United States	
Licensee	Lilly	United States	
Licensee	Mitsubishi Pharma	Japan	Japan; Far East
Other	Chiron	United States	

L41 ANSWER 28 OF 36 PHAR COPYRIGHT 2004 PJB on STN

AN 29819 PHAR

DN 035871

CN ciluprevir

CN BILN-2061

CN Cyclopropa(e)pyrrolo(1,2-a)(1,4)diazacyclopentadecine-14a(5H)-carboxylic acid, 6-(((cyclopentyloxy)carbonyl)amino)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-((7-methoxy-2-(2-((1-methylethyl)amino)-4-thiazolyl)-4-quinolinyl)oxy)-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)-

RN 300832-84-2

STA Active

CO

Type	Company Name (Country)	Development Status
Originator	Boehringer Ingelheim (Germany)	Phase II Clinical Trial

SO Pharmaprojects. PJB Publications Ltd., Richmond, Surrey, UK

TX **Ciluprevir (BILN-2061)** is a selective inhibitor of the hepatitis-C virus (HCV) NS3 serine protease, under development by Boehringer Ingelheim for the treatment of HCV infection (53rd Meet Am Assoc Study Liv Dis (Boston), 2002, Abs 464). Clinical Phase III trials are expected by the end of 2004 (18th Int Symp Med Chem (Copenhagen), 2004, Abs L29). Phase II It is in Phase II trials (Nature Rev Drug Disc, 2002, 1, 867). Phase II In healthy males, single doses of 5-2400mg po produced no serious adverse effects. The MTD was 2000mg; higher doses caused minor intestinal adverse effects. It had a pharmacokinetic profile suitable for bid dosing of >200mg with or without food (53rd Meet Am Assoc Study Liv Dis (Boston), 2002, Abs 800). In 31 patients with HCV genotype 1 infection and minimal liver fibrosis (mean age 47yr; 48% HCV treatment-naive), 7/9 subjects given **ciluprevir** 25mg po bid x2 days, 8/8 given 200 and 8/8 receiving 500mg po bid x2 days showed a >1log decrease in serum HCV RNA levels. Levels returned to baseline 1-7 days after stopping therapy. No difference was seen in responsiveness of interferon-naive and interferon-resistant patients. No safety issues were identified (ibid, Abs 866). In a randomized, double-blind, placebo-controlled study in 10 patients with HCV genotype 1 and significant liver fibrosis, **ciluprevir** 200mg po bid x2 days produced >2log reduction in serum HCV RNA levels in all 8 patients treated. 2 patients had a decrease of >3log (ibid, Abs 563). In a randomized study, 10 HCV genotype 2- and 3- patients with minimal or no liver fibrosis were given **ciluprevir** 500mg po bid po solution or placebo x2 days, with 12-day follow-up. 4/8 patients given **ciluprevir** showed a 1log reduction in HCV RNA, with no detectable difference between genotypes. A further **ciluprevir**-treated patient had a weak response. There were no safety issues (53rd Meet Am Assoc Study Liver Dis (Boston), 2003). Preclinical In the cell-based replicon assay it showed inhibition of HCV RNA replication at low nM levels. It is orally bioavailable in various animal species. It had Ki values of 0.3 and 0.66nM for the NS3 proteases of HCV genotypes 1a and 1b, respectively (ibid, Abs 464). Updated by AZ on 16/8/2004.

DSTA World: Phase II Clinical Trial  
Germany: Phase II Clinical Trial

CC J5Z Antiviral, other

CT Indication: Infection, hepatitis-C virus

ORGM CH-SY (Chemical, synthetic)

RTE A-PO (Alimentary, po)

RDAT 20040120 RNTE ##Act##Name Granted **BILN-2061**  
20030515 ##Act##New Chemical Structure New  
20030509 ##Act##New Product

NRAT 6:Novelty Rating - Leading Compound

MRAT 3:Market Rating - US\$ 2001-5000 million

SRAT 0:Speed Rating - Not available

TRAT 0:Total Rating - Total Rating unavailable

PHCD PR-NS3-AN; NS3 protease inhibitor; Enzyme, Hydrolase, NS3 protease inhibitor; NS3-4A protease inhibitor; Protease inhibitor, NS3; E-HY-PR-NS3-AN; 3.4.21.

PHCD E; E-AN; E-HY; E-HY-AN; E-HY-PR; E-HY-PR-AN; E-HY-PR-NS3; E-HY-PR-NS3-AN; HY; HY-AN; HY-PR; HY-PR-AN; HY-PR-NS3; HY-PR-NS3-AN; PR; PR-AN; PR-NS3; PR-NS3-AN; NS3; NS3-AN.

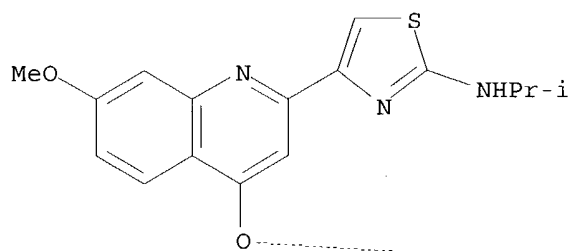
PHK Model	Parameter	Values	Units
Human (po)	MTD	2000	mg

LN Therapy (CC)	Pharmacology (PHCD)	Status (DSTC)
J5Z	PR-NS3-AN	C2

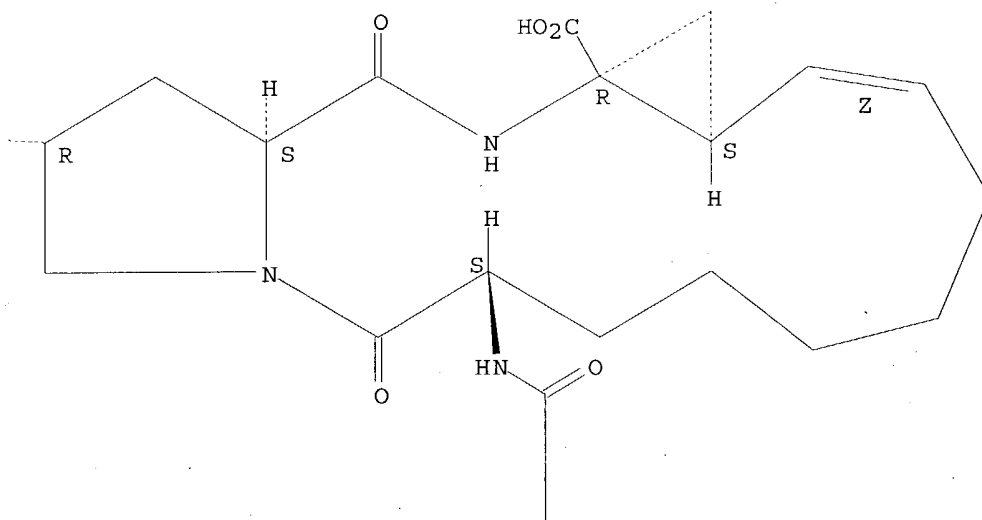
LCDAT 20040816: AZ : Phase III plans reported at 18th ISMC

Absolute stereochemistry.  
Double bond geometry as shown.

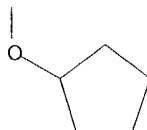
PAGE 1-A



PAGE 1-B



PAGE 2-B



L41 ANSWER 29 OF 36 PHAR COPYRIGHT 2004 PJB on STN  
 AN 15090 PHAR  
 DN 026229  
 CN VX-950  
 CN Pharmaprojects No. 5437  
 CN HCV protease inhib, Lilly  
 CN LY-570310  
 CN HCV protease inhib, Vertex  
 STA Active

CO

Type	Company Name (Country)	Development Status
Originator	Vertex Pharmaceuticals (United States)	Phase I Clinical Trial
Licensee	Mitsubishi Pharma (Japan)	Preclinical

SO Pharmaprojects. PJB Publications Ltd., Richmond, Surrey, UK  
 TX VX-950 is an NS3-4A serine protease inhibitor, under development by Vertex Pharmaceuticals for the treatment of chronic hepatitis- C virus (HCV) infection. Marketing VX-950 was identified as part of a collaboration between Vertex and Lilly, and was to be co-promoted in the US, with Lilly responsible for formulation, global marketing and development (Ann Rep, Vertex, 1999). However, the agreement was restructured and Vertex will lead development and commercialization, with Lilly retaining a financial interest (Press release, Vertex, 2 Jan 2003). It is exclusively licensed to Mitsubishi Pharma for development and commercialization in Japan and certain Far Eastern countries (Press release, Vertex, 14 Jun 2004). Chiron was granted limited rights to review VX-950 for licensing (Press release, Chiron, 7 Nov 2003). Clinical Phase IA placebo-controlled Phase Ib trial to evaluate the safety, tolerability and pharmacokinetics of up to 14 days of dosing with VX-950 in healthy volunteers and HCV-infected patients is expected in the 4th qtr of 2004, with results expected in the 1st half of 2005 (Press release, Vertex, 7 Sep 2004; 17th Bear Stearns Healthcare Conf (New York), 2004). In a Phase Ia trial in 35 healthy subjects in Europe to assess safety, tolerability and pharmacokinetics in escalating single doses, VX-950 25-1250mg did not reach MTD and no DLTs were identified. However, blood concentrations of VX-950 exceeded levels showing antiviral activity in preclinical studies, and at certain doses these concentrations were maintained for >12hr. Analysis of clinical and preclinical pharmacokinetics suggests liver concentrations 10-30x above the replicon IC50 were achievable in humans (Press release, Vertex, 7 Sep 2004). Preclinical In an HCV replicon assay system, treatment of HCV replicon cells with VX-950 x9 days reduced HCV RNA by almost 10000x. HCV replicon cells treated with VX-950 x13 days exhibited viral clearance at day 13, and no rebound of HCV RNA was observed at day 27. In a novel HCV protease expression model, VX-950 po resulted in a significant, dose-dependent inhibition of an HCV-protease

enzyme-dependent signal. In untreated controls, high concentrations of active HCV protease enzyme over 7 days were associated with significant liver damage; however, treatment with VX-950 for the initial 3 days resulted in sharply reduced liver damage. VX-950 was also able to inhibit HCV replicons containing the dominant mutation observed for **BILN-2061** (qv) to the same degree as wild-type replicons (Press release, Vertex, 27 Oct 2003). Updated by AG on 29/9/2004.

DSTA World: Phase I Clinical Trial

Japan: Preclinical

United States: Preclinical

CC J5Z Antiviral, other

CT Indication: Infection, hepatitis-C virus

ORGM CH-SY (Chemical, synthetic)

RTE A-PO (Alimentary, po)

RDAT 20040614 RNTE ##Act##New Licensee Mitsubishi Pharma

20040609 ##Act##Status changed Phase I Clinical Trial

20020107 ##Act##Compound identified HCV protease inhib, Vertex

20001009 ##Act##Development Continuing

19990914 ##Est##No Development Reported

19970718 ##Est##New Product

NRAT 5:Novelty Rating - 2nd, 3rd or 4th Compound

MRAT 3:Market Rating - US\$ 2001-5000 million

SRAT 2:Speed Rating - Slower than Average

TRAT 10:Total Rating - Total Rating

PHCD PR-NS3-AN; NS3 protease inhibitor; Enzyme, Hydrolase, NS3 protease inhibitor; NS3-4A protease inhibitor; Protease inhibitor, NS3; E-HY-PR-NS3-AN; 3.4.21.

PHCD E; E-AN; E-HY; E-HY-AN; E-HY-PR; E-HY-PR-AN; E-HY-PR-NS3;

E-HY-PR-NS3-AN; HY; HY-AN; HY-PR; HY-PR-AN; HY-PR-NS3; HY-PR-NS3-AN;

PR; PR-AN; PR-NS3; PR-NS3-AN; NS3; NS3-AN.

LN

Therapy (CC) | Pharmacology (PHCD) | Status (DSTC)

=====+=====+=====

J5Z | PR-NS3-AN | C1

LCDAT 20040929: AG : Expected timing of results from planned Phase IIb trial reported

STRUCTURE DIAGRAM IS NOT AVAILABLE

=> d ibib abs 30-31

L41 ANSWER 30 OF 36 TOXCENTER COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:53173 TOXCENTER

COPYRIGHT: Copyright (c) 2004 The Thomson Corporation.

DOCUMENT NUMBER: PREV200400116586

TITLE: Antiviral effect of **BILN 2061**, a novel

HCV serine protease inhibitor, after oral treatment over 2 days in patients with chronic hepatitis C, non-genotype 1

AUTHOR(S): Reiser, Markus [Reprint Author]; Hinrichsen, Holger;

Benhamou, Yves; Sentjens, Roel; Wedemeyer, Heiner;

Calleja, Luis; Forns, Xavier; Croenlein, Jens; Yong, Chan;

Nehmiz, Gerhard; Steinmann, Gerhard

CORPORATE SOURCE: Medizinische Universitaetsklinik, Bochum, Germany

SOURCE: Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp.

221A. print.

Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases Boston, MA, USA October 24-28, 2003 American Association for the Study of Liver Diseases.

ISSN: 0270-9139 (ISSN print).

DOCUMENT TYPE:

Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

FILE SEGMENT:

BIOSIS

OTHER SOURCE:

BIOSIS 2004:123272

LANGUAGE:

English

ENTRY DATE:

Entered STN: 20040309

Last Updated on STN: 20040309

AB Introduction: **BILN 2061** is a potent and specific inhibitor of the HCV serine protease in-vitro and in patients infected with genotype 1 (GT 1) as recently reported. In a first exploratory trial, the effect of a 2-day oral treatment with **BILN 2061** was investigated in GT 2 and GT 3 patients with minimal liver fibrosis. Methods: In a randomized, double-blind group comparison, 10 male patients with HCV other than GT 1 (InnoLiPA) and no or minimal liver fibrosis (Ishak 0-2) were administered 500 mg **BILN 2061** or placebo in an oral solution (randomized 8:2) b.i.d. over 2 days. Virus load (VL) was measured as HCV RNA by Cobas Amplicor HCV Monitor v2.0. Results: Mean age of all 10 patients was 37+-7 years. HCV genotypes were GT 2 (3 patients) and GT 3 (7 patients). 9/10 patients were naive for anti-HCV therapy. All patients completed the study and were followed up for 12+-2 days. VL decreased by gtoreq1 LOG10 unit in 4/8 patients treated with 500mg **BILN 2061** b.i.d., without detectable difference between GTs 2 and 3. A weak response was observed in 1 **BILN 2061**-treated patient, whereas 3/8 **BILN 2061**-treated patients and 2/2 patients given placebo experienced no response. The largest VL decrease was observed in the one patient with GT 2 HCV that had been previously treated with anti-HCV therapy. However HCV-RNA was still detectable. After end of treatment, VL returned to baseline levels within 1-7 days. No adverse events were reported. Liver function tests did not change during treatment. Vital signs, routine laboratory and ECG did not show relevant drug-induced changes. Tolerability was rated "good" by the investigators in 9 patients and "satisfactory" in 1 **BILN 2061**-treated patient. Conclusion: **BILN 2061**, given p.o. over 2 days at 500 mg b.i.d., demonstrated antiviral activity in 5/8 non-GT-1 in patients. In contrast to our previous results in GT-1 patients, the antiviral activity was not uniform and less pronounced. No safety issues were identified among the 8 patients exposed to **BILN 2061**.

L41 ANSWER 31 OF 36 TOXCENTER COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:277977 TOXCENTER

COPYRIGHT: Copyright (c) 2004 The Thomson Corporation.

DOCUMENT NUMBER: PREV200200618388

TITLE: Tolerability and pharmacokinetics of **BILN**

**2061**, a novel HCV serine protease inhibitor, after oral single doses of 5 to 2400 mg in healthy male subjects Narjes, Hans [Reprint author]; Yong, Chan Loi; Staehle, Hildegard [Reprint author]; Steinmann, Gerhard [Reprint author]

CORPORATE SOURCE: Boehringer Ingelheim Pharma KG, Biberach, Germany

SOURCE: Hepatology, (October, 2002) Vol. 36, No. 4 Part 2, pp. 363A. print.

Meeting Info.: 53rd Annual Meeting on the Liver BOSTON,

MA, USA November 01-05, 2002  
CODEN: HPTLD9. ISSN: 0270-9139.  
DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
FILE SEGMENT: BIOSIS  
OTHER SOURCE: BIOSIS 2002:618388  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20021210  
Last Updated on STN: 20021210

=> d ibib abs 32-

YOU HAVE REQUESTED DATA FROM 5 ANSWERS - CONTINUE? Y/(N):y

L41 ANSWER 32 OF 36 USPATFULL on STN

ACCESSION NUMBER: 2004:240310 USPATFULL  
TITLE: Viral polymerase inhibitors  
INVENTOR(S): Poupart, Marc-Andre, Laval, CANADA  
Beaulieu, Pierre Louis, Rosemere, CANADA  
Rancourt, Jean, Laval, CANADA  
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Ingelheim,  
GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004186125	A1	20040923
APPLICATION INFO.:	US 2004-755544	A1	20040112 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-441674P	20030122 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	BOEHRINGER INGELHEIM CORPORATION, 900 RIDGEBURY RD, P O BOX 368, RIDGEFIELD, CT, 06877	
NUMBER OF CLAIMS:	42	
EXEMPLARY CLAIM:	1	
LINE COUNT:	2152	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
AB	An isomer, enantiomer, diastereoisomer or tautomer of a compound, represented by formula I: ##STR1##	

wherein wherein A, B, R.sup.2, R.sup.3, M.sup.1, M.sup.2, M.sup.3,  
M.sup.4, Y.sup.1 and Z are as defined in claim 1, or a salt thereof, as  
an inhibitor of HCV NS5B polymerase.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L41 ANSWER 33 OF 36 USPATFULL on STN

ACCESSION NUMBER: 2004:221854 USPATFULL  
TITLE: Viral polymerase inhibitors  
INVENTOR(S): Beaulieu, Pierre Louis, Rosemere, CANADA  
Brochu, Christian, Blainville, CANADA  
Chabot, Catherine, Terrebonne, CANADA  
Jolicoeur, Eric, Laval, CANADA  
Kawai, Stephen, Montreal, CANADA  
Poupart, Marc-Andre, Laval, CANADA  
Tsantrizos, Youla S., St. Laurent, CANADA  
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Ingelheim,  
GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004171626	A1	20040902
APPLICATION INFO.:	US 2004-755256	A1	20040112 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-441871P	20030122 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	BOEHRINGER INGELHEIM CORPORATION, 900 RIDGEBURY RD, P O BOX 368, RIDGEFIELD, CT, 06877	
NUMBER OF CLAIMS:	76	
EXEMPLARY CLAIM:	1	
LINE COUNT:	6508	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An isomer, enantiomer, diastereoisomer or tautomer of a compound, represented by formula I: ##STR1##

wherein wherein A, B, R.sup.2, R.sup.3, L, M.sup.1, M.sup.2, M.sup.3, M.sup.4, Y.sup.1, Y.sup.0, Z and Sp are as defined in claim 1, or a salt thereof, as an inhibitor of HCV NS5B polymerase.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L41 ANSWER 34 OF 36 USPATFULL on STN

ACCESSION NUMBER: 2004:108172 USPATFULL

TITLE: Compounds with the bicyclo[4.2.1]nonane system for the treatment of flaviviridae infections

INVENTOR(S): Wang, Peiyuan, Lilburn, GA, UNITED STATES  
Stuyver, Lieven J., Snellville, GA, UNITED STATES  
Watanabe, Kyoichi A., Stone Mountain, GA, UNITED STATES  
Hassan, Abdalla, Chamblee, GA, UNITED STATES  
Chun, Byoung-Kwon, Duluth, GA, UNITED STATES  
Hollecker, Laurent, Atlanta, GA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004082574	A1	20040429
APPLICATION INFO.:	US 2003-632997	A1	20030801 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-453716P	20020801 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	KING & SPALDING, 191 PEACHTREE STREET, N.E., ATLANTA, GA, 30303-1763	
NUMBER OF CLAIMS:	24	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	1 Drawing Page(s)	
LINE COUNT:	3637	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The disclosed invention is a bicyclo[4.2.1]nonane and its pharmaceutically acceptable salt or prodrug, and its composition and method of use to treat Flaviviridae (Hepacivirus, Flavivirus, and Pestivirus) infections in a host, including animals, and especially humans.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L41 ANSWER 35 OF 36 USPATFULL on STN

ACCESSION NUMBER: 2004:101717 USPATFULL  
TITLE: 2'-C-methyl-3'-O-L-valine ester ribofuranosyl cytidine  
for treatment of flaviviridae infections  
INVENTOR(S): Sommadossi, Jean-Pierre, Cambridge, MA, UNITED STATES  
LaColla, Paola, Cagliari, ITALY

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004077587	A1	20040422
APPLICATION INFO.:	US 2003-607909	A1	20030627 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-392351P	20020628 (60)
	US 2003-466194P	20030428 (60)
	US 2003-470949P	20030514 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	KING & SPALDING, 191 PEACHTREE STREET, N.E., ATLANTA, GA, 30303-1763	
NUMBER OF CLAIMS:	45	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	12 Drawing Page(s)	
LINE COUNT:	3396	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The 3'-L-valine ester of  $\beta$ -D-2'-C-methyl-ribofuranosyl cytidine provides superior results against flaviviruses and pestiviruses, including hepatitis C virus. Based on this discovery, compounds, compositions, methods and uses are provided for the treatment of flaviviridae, including HCV, that include the administration of an effective amount of val-mCyd or its salt, ester, prodrug or derivative, optionally in a pharmaceutically acceptable carrier. In an alternative embodiment, val-mCyd is used to treat any virus that replicates through an RNA-dependent RNA polymerase.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L41 ANSWER 36 OF 36 USPATFULL on STN

ACCESSION NUMBER: 2004:88901 USPATFULL  
TITLE: 2', 3'-Dideoxynucleoside analogues for the treatment or  
prevention of Flaviviridae infections  
INVENTOR(S): Schinazi, Raymond F., Decatur, GA, UNITED STATES  
Striker, Robert, Madison, WI, UNITED STATES  
Shi, Junxing, Duluth, GA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004067877	A1	20040408
APPLICATION INFO.:	US 2003-632875	A1	20030801 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-453715P	20020801 (60)
	US 2002-453716P	20020801 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	KING & SPALDING, 191 PEACHTREE STREET, N.E., ATLANTA,	

GA, 30303-1763  
NUMBER OF CLAIMS: 60  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 5 Drawing Page(s)  
LINE COUNT: 2416  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for the treatment or prevention of Flaviviridae infections, in particular, hepatitis C virus infection, in a host, and in particular, a human, is provided that includes administering an effective amount of a  $\beta$ -L- or  $\beta$ -D-2',3'-dideoxynucleoside or a pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable diluent or excipient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> FIL STNGUIDE

FILE 'STNGUIDE' ENTERED AT 12:28:47 ON 13 OCT 2004  
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT  
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE  
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.  
LAST RELOADED: Oct 8, 2004 (20041008/UP).

FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 12:29:24 ON 13 OCT 2004  
=> => d que l43

L6 1 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/RN  
L7 0 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/CRN  
L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON (L6 OR L7)  
L16 SEL PLU=ON L8 1- CHEM : 4 TERMS  
L17 74 SEA L16  
L42 61 DUP REM L17 (13 DUPLICATES REMOVED)  
L43 4 SEA L42 AND ?CRYST?

=>

=> d ibib abs hit l43  
YOU HAVE REQUESTED DATA FROM FILE 'EMBASE' - CONTINUE? (Y)/N:y

L43 ANSWER 1 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2003468113 EMBASE  
TITLE: Current therapy and new molecular approaches to antiviral  
treatment and prevention of hepatitis C.  
AUTHOR: Hugle T.; Cerny A.  
CORPORATE SOURCE: Dr. A. Cerny, Clinica Medica, Ospedale Civico, CH-6903  
Lugano, Switzerland. andreas.cerny@bluewin.ch  
SOURCE: Reviews in Medical Virology, (2003) 13/6 (361-371).  
Refs: 79  
ISSN: 1052-9276 CODEN: RMVIEW  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 004 Microbiology  
030 Pharmacology  
037 Drug Literature Index

038 Adverse Reactions Titles  
039 Pharmacy

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Current therapeutic options for hepatitis C are limited, especially for genotype 1. For genotypes 2 and 3, pegylated interferon in combination with ribavirin, can lead to a sustained virological response in up to 80% of patients. Unfortunately, adverse effects of IFN and ribavirin are a major problem and the list of contraindications for HCV therapy is long, including decompensated cirrhosis of the liver and psychiatric disorders. Therefore, alternative therapeutic approaches are needed. New delivery options for IFN and ribavirin are aimed at optimising efficiency and reducing adverse effects. Recent progress in the molecular virology of HCV has identified new targets for antiviral intervention. Inhibition of HCV gene expression and replication as well as immunotherapeutic concepts aimed at enhancing the cellular immune response against HCV are being explored. Solution of the **crystal** structures of HCV key enzymes led to the design of specific inhibitors including compounds active against the well characterised NS3 serine protease and RNA-dependent RNA polymerase which are currently in the early phase clinical investigation. New strategies for inhibiting HCV gene expression include the use of antisense oligodeoxynucleotides and ribozymes. Immunomodulation by agents such as inosine monophosphate dehydrogenase inhibitors, thymosin-alpha 1, histamine or amantadine are being studied in combination with IFN and/or ribavirin. Immunotherapeutic vaccination with recombinant HCV E1 protein improved host immunity against HCV and thus seems to be a promising new option. Copyright .COPYRGT. 2003 John Wiley & Sons, Ltd.

AB Current therapeutic options for hepatitis C are limited, especially for genotype 1. For genotypes 2 and 3, pegylated interferon in combination with ribavirin, can lead to a sustained virological response in up to 80% of patients. Unfortunately, adverse effects of IFN and ribavirin are a major problem and the list of contraindications for HCV therapy is long, including decompensated cirrhosis of the liver and psychiatric disorders. Therefore, alternative therapeutic approaches are needed. New delivery options for IFN and ribavirin are aimed at optimising efficiency and reducing adverse effects. Recent progress in the molecular virology of HCV has identified new targets for antiviral intervention. Inhibition of HCV gene expression and replication as well as immunotherapeutic concepts aimed at enhancing the cellular immune response against HCV are being explored. Solution of the **crystal** structures of HCV key enzymes led to the design of specific inhibitors including compounds active against the well characterised NS3 serine protease and RNA-dependent RNA polymerase which are currently in the early phase clinical investigation. New strategies for inhibiting HCV gene expression include the use of antisense oligodeoxynucleotides and ribozymes. Immunomodulation by agents such as inosine monophosphate dehydrogenase inhibitors, thymosin-alpha 1, histamine or amantadine are being studied in combination with IFN and/or ribavirin. Immunotherapeutic vaccination with recombinant HCV E1 protein improved host immunity against HCV and thus seems to be a promising new option. Copyright .COPYRGT. 2003 John Wiley & Sons, Ltd.

CT Medical Descriptors:

- \*hepatitis C: DT, drug therapy
- \*hepatitis C: ET, etiology
- \*hepatitis C: PC, prevention
- \*infection prevention
- virus gene
- genotype
- drug response
- drug contraindication
- drug delivery system

side effect: SI, side effect  
gene expression  
drug targeting  
immunotherapy  
enzyme structure  
**crystal structure**  
drug design  
drug activity  
antiviral activity  
protein targeting  
immunomodulation  
vaccination  
Hepatitis C virus  
immune response  
cellular immunity  
hemolytic anemia: SI, side effect  
mental disease: SI, side effect  
flu like syndrome: SI, side effect  
leukopenia: SI, side effect  
thrombocytopenia: SI, side effect  
teratogenicity  
virus replication  
drug hypersensitivity: SI, side effect  
rash: SI, side effect  
human  
nonhuman  
clinical trial  
review  
Drug Descriptors:  
alpha interferon: AE, adverse drug reaction  
alpha interferon: CT, clinical trial  
alpha interferon: CB, drug combination  
alpha interferon: DT, drug therapy  
alpha interferon: TO, drug toxicity  
alpha interferon: PR, pharmaceuticals  

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alpha interferon: PD, pharmacology  
alpha interferon: SC, subcutaneous drug administration  
ribavirin: AE, adverse drug reaction  
ribavirin: CT, clinical trial  
ribavirin: CB, drug combination  
ribavirin: CM, drug comparison  
ribavirin: DT, drug therapy  
ribavirin: PK, pharmacokinetics  
ribavirin: PD, pharmacology  
ribavirin: PO, oral drug administration  
albumin conjugate: PR, pharmaceuticals  
liposome: PR, pharmaceuticals  
polyaminoacid: PR, pharmaceuticals  
polyaminoacid: PO, oral drug administration  
ribavirin derivative: AE, adverse drug reaction  
ribavirin derivative: CT, clinical trial  
ribavirin derivative: CB, drug combination  
ribavirin derivative: CM, drug comparison  
ribavirin derivative: DT, drug therapy  
ribavirin derivative: PD, pharmacology  
viramidine: AE, adverse drug reaction  
viramidine: CT, clinical trial  
viramidine: CB, drug combination  
viramidine: CM, drug comparison  
viramidine: DT, drug therapy

viramidine: PD, pharmacology  
levovirin: AE, adverse drug reaction  
levovirin: CT, clinical trial  
levovirin: CM, drug comparison  
levovirin: DT, drug therapy  
levovirin: PD, pharmacology  
proteinase inhibitor: AE, adverse drug reaction  
proteinase inhibitor: CT, clinical trial  
proteinase inhibitor: DO, drug dose  
proteinase inhibitor: DT, drug therapy  
proteinase inhibitor: PK, pharmacokinetics  
proteinase inhibitor: PD, pharmacology  
proteinase inhibitor: PO, oral drug administration  
    biln 2061: AE, adverse drug reaction  
    biln 2061: CT, clinical trial  
    biln 2061: DO, drug dose  
    biln 2061: DT, drug therapy  
    biln 2061: PK, pharmacokinetics  
    biln 2061: PD, pharmacology  
    biln 2061: PO, oral drug administration  
vx 950: DT, drug therapy  
vx 950: PD, pharmacology  
virus protein  
protein NS5B  
RNA directed DNA polymerase inhibitor: CT, clinical trial  
RNA directed DNA polymerase inhibitor: DT, drug therapy  
RNA directed DNA polymerase inhibitor: PD, pharmacology  
jtk 003: CT, clinical trial  
jtk 003: DT, drug therapy  
jtk 003: PD, pharmacology  
ribozyme: AE, adverse drug reaction  
ribozyme: CT, clinical trial  
ribozyme: DT, drug therapy  
ribozyme: TO, drug toxicity  
ribozyme: PD, pharmacology  
hepatozyme: AE, adverse drug reaction  
hepatozyme: CT, clinical trial  
hepatozyme: DT, drug therapy  
hepatozyme: TO, drug toxicity  
hepatozyme: PD, pharmacology  
antisense oligodeoxynucleotide: CT, clinical trial  
antisense oligodeoxynucleotide: DT, drug therapy  
antisense oligodeoxynucleotide: PD, pharmacology  
isis 14803: CT, clinical trial  
isis 14803: DT, drug therapy  
isis 14803: PD, pharmacology  
RNA derivative: DV, drug development  
RNA derivative: DT, drug therapy  
RNA derivative: PD, pharmacology  
small interfering rna: DV, drug development  
small interfering rna: DT, drug therapy  
small interfering rna: PD, pharmacology  
monoclonal antibody: DT, drug therapy  
monoclonal antibody: PD, pharmacology  
xtl 002: DT, drug therapy  
xtl 002: PD, pharmacology  
cicavir: DT, drug therapy  
cicavir: PD, pharmacology  
immunomodulating agent: CB, drug combination  
immunomodulating agent: DT, drug therapy

thymosin alphas: CT, clinical trial  
 thymosin alphas: CB, drug combination  
 thymosin alphas: DO, drug dose  
 thymosin alphas: DT, drug therapy  
 thymosin alphas: PD, pharmacology  
 inosinate dehydrogenase inhibitor: CB, drug combination  
 inosinate dehydrogenase inhibitor: DT, drug therapy  
 inosinate dehydrogenase inhibitor: PD, pharmacology  
 merimepodib: CT, clinical trial  
 merimepodib: CB, drug combination  
 merimepodib: DT, drug therapy  
 merimepodib: PD, pharmacology  
 unindexed drug  
 unclassified drug

CN (1) Vx 950; (2) Jtk 003; **Biln 2061**; Isis 14803; Xtl 002

=> d ibib abs hit 143 2-

YOU HAVE REQUESTED DATA FROM FILE 'EMBASE' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):y

L43 ANSWER 2 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2003337607 EMBASE

TITLE: Hepatitis C virus NS3 serine protease as a drug discovery target.

AUTHOR: McPhee F.; Yeung K.-S.; Good A.C.; Meanwell N.A.

CORPORATE SOURCE: K.-S. Yeung, B.-Myers Squibb Pharmaceut. Res. I., 5  
Research Parkway, Wallingford, CT 06492, United States.  
kapsun.yeung@bms.com

SOURCE: Drugs of the Future, (1 May 2003) 28/5 (465-488).  
Refs: 196  
ISSN: 0377-8282 CODEN: DRFUD4

COUNTRY: Spain

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 004 Microbiology  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Hepatitis C virus NS3 serine protease (HCV Pr) is an extensively studied enzyme for drug intervention. The target presented serious challenges in early screening efforts, however, with the lack of prominent active site features rendering traditional nonpeptidic serine protease inhibitor motifs and high-throughput screening campaigns ineffectual. In contrast, the peptidomimetic structure-based design approach has proven successful in the discovery of potent inhibitors of HCV Pr. Subsequent rational design efforts have led to the identification of an inhibitor that demonstrates efficacy in man, validating the years of research. This review summarizes why HCV Pr provides a viable drug discovery target despite the many obstacles, and details the breakthroughs in protein production and assay development that have facilitated inhibitor advances. The latest inhibitors in preclinical and clinical research and development are also presented, along with a discussion of how the recent HCV Pr clinical candidate challenges much of the dogma surrounding peptidomimetic design. In addition, future issues such as resistance, genotype coverage and HIV-HCV coinfecting individuals are considered.

CT Medical Descriptors:

\*drug targeting  
\*Hepatitis C virus  
drug screening  
enzyme active site  
drug efficacy  
protein analysis  
inhibition kinetics  
drug research  
drug design  
genotype  
drug structure  
structure activity relation  
in vitro study  
enzyme structure  
enzyme analysis  
drug protein binding  
binding kinetics  
binding affinity  
protein motif  
nuclear magnetic resonance  
protein expression  
molecular weight  
protein modification  
protein degradation  
    **X ray crystallography**  
        **crystal structure**  
enzyme conformation  
sequence homology  
human  
nonhuman  
clinical trial  
review  
Drug Descriptors:  
\*serine proteinase  
\*virus protein: EC, endogenous compound  
\*NS3 protein: EC, endogenous compound  
serine proteinase inhibitor: CT, clinical trial  
serine proteinase inhibitor: AN, drug analysis  
serine proteinase inhibitor: PD, pharmacology  
proteinase inhibitor: CT, clinical trial  
proteinase inhibitor: AN, drug analysis  
proteinase inhibitor: PD, pharmacology  
antivirus agent: CT, clinical trial  
antivirus agent: AN, drug analysis  
antivirus agent: PD, pharmacology  
    **biln 2061: CT, clinical trial**  
    **biln 2061: AN, drug analysis**  
    **biln 2061: PD, pharmacology**  
wo 0248172: AN, drug analysis  
wo 0248172: DV, drug development  
wo 0208244: AN, drug analysis  
wo 0208244: DV, drug development  
wo 0208198: AN, drug analysis  
wo 0208198: DV, drug development  
wo 0181325: AN, drug analysis  
wo 0181325: DV, drug development  
wo 0208187: AN, drug analysis  
wo 0208187: DV, drug development  
wo 0177113: AN, drug analysis  
wo 0177113: DV, drug development

wo 0218369: AN, drug analysis  
 wo 0218369: DV, drug development  
 wo 03006490: AN, drug analysis  
 wo 03006490: DV, drug development  
 wo 0174768: AN, drug analysis  
 wo 0174768: DV, drug development  
 leukocyte elastase inhibitor: AN, drug analysis  
 leukocyte elastase inhibitor: DV, drug development  
 leukocyte elastase inhibitor: PK, pharmacokinetics  
 leukocyte elastase inhibitor: PO, oral drug administration  
 tryptase inhibitor: AN, drug analysis  
 tryptase inhibitor: DV, drug development  
 apc 6336: AN, drug analysis  
 apc 6336: DV, drug development  
 cra 6336: AN, drug analysis  
 cra 6336: DV, drug development  
 imidazole derivative: AN, drug analysis  
 imidazole derivative: DV, drug development  
 unclassified drug

CN (1) Wo 0248172; (2) Wo 0208244; (3) Wo 0208198; (4) Wo 0181325; (5) Wo 0208187; (6) Wo 0177113; (7) Wo 0218369; (8) Wo 03006490; (9) Wo 0174768;  
**Biln 2061; Apc 6336; Cra 6336**

L43 ANSWER 3 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2003318276 EMBASE  
 TITLE: Promising candidates for the treatment of chronic hepatitis C.  
 AUTHOR: Walker M.P.; Yao N.; Hong Z.  
 CORPORATE SOURCE: Z. Hong, Drug Discovery, Ribapharm Inc., 3300 Hyland Avenue, Costa Mesa, CA 92626, United States  
 SOURCE: Expert Opinion on Investigational Drugs, (1 Aug 2003) 12/8 (1269-1280).  
 Refs: 113  
 ISSN: 1354-3784 CODEN: EOIDER

COUNTRY: United Kingdom  
 DOCUMENT TYPE: Journal; General Review  
 FILE SEGMENT: 004 Microbiology  
 030 Pharmacology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 048 Gastroenterology  
 052 Toxicology

LANGUAGE: English  
 SUMMARY LANGUAGE: English

AB Chronic hepatitis C virus (HCV) infection is the cause of an emerging global pandemic of chronic liver disease. Current pegylated IFN- $\alpha$ /ribavirin combination therapies are merely 54 - 56% efficacious and are often poorly tolerated. Popular strategies to improve upon existing therapies include efforts to decrease the dosing regime, improve the safety profile and specifically target the liver, the site of HCV replication. A clear goal of novel therapies is to significantly improve the therapeutic response for HCV-infected patients. One popular scheme to accomplish this is to directly target the viral enzymes involved in HCV RNA replication. While peptidomimetics have been pursued as potent and specific inhibitors of the serine protease, nucleoside analogues and non-nucleoside small molecules have been explored as RNA-dependent RNA polymerase inhibitors with promising potential. Advances in the understanding of HCV replication at the molecular level that stem from the use of the subgenomic replicon system, in vitro enzyme assays and from co-

**crystallographic** structure solutions of the replication enzymes with novel inhibitors have propelled these compounds into clinical development. As these candidates are developed further, there is great hope for a cure for all those chronically infected with HCV.

AB Chronic hepatitis C virus (HCV) infection is the cause of an emerging global pandemic of chronic liver disease. Current pegylated IFN- $\alpha$ /ribavirin combination therapies are merely 54 - 56% efficacious and are often poorly tolerated. Popular strategies to improve upon existing therapies include efforts to decrease the dosing regime, improve the safety profile and specifically target the liver, the site of HCV replication. A clear goal of novel therapies is to significantly improve the therapeutic response for HCV-infected patients. One popular scheme to accomplish this is to directly target the viral enzymes involved in HCV RNA replication. While peptidomimetics have been pursued as potent and specific inhibitors of the serine protease, nucleoside analogues and non-nucleoside small molecules have been explored as RNA-dependent RNA polymerase inhibitors with promising potential. Advances in the understanding of HCV replication at the molecular level that stem from the use of the subgenomic replicon system, in vitro enzyme assays and from **crystallographic** structure solutions of the replication enzymes with novel inhibitors have propelled these compounds into clinical development. As these candidates are developed further, there is great hope for a cure for all those chronically infected with HCV.

CT Medical Descriptors:

\*hepatitis C: DT, drug therapy

\*hepatitis C: ET, etiology

Hepatitis C virus

chronic liver disease: DT, drug therapy

chronic liver disease: ET, etiology

drug efficacy

drug tolerability

dose response

drug safety

drug targeting

virus replication

drug response

RNA replication

molecular mechanics

replicon

in vitro study

enzyme assay

**crystallography**

**crystal structure**

monotherapy

drug approval

food and drug administration

drug absorption

drug clearance

drug half life

drug structure

antiviral activity

drug distribution

cytokine release

cytokine production

hemolytic anemia

fatigue: SI, side effect

depression: SI, side effect

skin manifestation: SI, side effect

human

nonhuman

review

Drug Descriptors:

\*antivirus agent: AE, adverse drug reaction  
\*antivirus agent: AN, drug analysis  
\*antivirus agent: DV, drug development  
\*antivirus agent: DO, drug dose  
\*antivirus agent: DT, drug therapy  
\*antivirus agent: TO, drug toxicity  
\*antivirus agent: PD, pharmacology  
\*antivirus agent: PO, oral drug administration  
\*antivirus agent: SC, subcutaneous drug administration  
alpha interferon: CB, drug combination  
alpha interferon: DT, drug therapy  
alpha interferon: PK, pharmacokinetics  
ribavirin: CB, drug combination  
ribavirin: DT, drug therapy  
virus enzyme: EC, endogenous compound  
virus RNA: EC, endogenous compound  
peptide derivative: AE, adverse drug reaction  
peptide derivative: AN, drug analysis  
peptide derivative: CB, drug combination  
peptide derivative: DV, drug development  
peptide derivative: DT, drug therapy  
peptide derivative: PD, pharmacology  
peptide derivative: SC, subcutaneous drug administration  
serine proteinase inhibitor: AN, drug analysis  
serine proteinase inhibitor: DV, drug development  
serine proteinase inhibitor: DT, drug therapy  
serine proteinase inhibitor: PD, pharmacology  
serine proteinase inhibitor: PO, oral drug administration  
    **biln 2061: AN, drug analysis**  
    **biln 2061: DV, drug development**  
    **biln 2061: DT, drug therapy**  
    **biln 2061: PD, pharmacology**  
    **biln 2061: PO, oral drug administration**

---

nucleoside analog: DV, drug development  
nucleoside analog: DT, drug therapy  
nucleoside analog: PD, pharmacology  
RNA directed DNA polymerase inhibitor: AN, drug analysis  
RNA directed DNA polymerase inhibitor: DV, drug development  
RNA directed DNA polymerase inhibitor: DT, drug therapy  
RNA directed DNA polymerase inhibitor: PD, pharmacology  
nm 283: AN, drug analysis  
nm 283: DV, drug development  
nm 283: DT, drug therapy  
nm 283: PD, pharmacology  
nm 107: DV, drug development  
nm 107: PK, pharmacokinetics  
nm 107: PD, pharmacology  
enzyme inhibitor: DV, drug development  
enzyme inhibitor: DT, drug therapy  
enzyme inhibitor: PD, pharmacology  
peginterferon alpha2a: CB, drug combination  
peginterferon alpha2a: DT, drug therapy  
peginterferon alpha2a: PK, pharmacokinetics  
recombinant alpha2a interferon: CB, drug combination  
recombinant alpha2a interferon: DT, drug therapy  
recombinant alpha2a interferon: PK, pharmacokinetics  
recombinant alpha2b interferon: CB, drug combination  
recombinant alpha2b interferon: DT, drug therapy

recombinant alpha2b interferon: PK, pharmacokinetics  
 consensus interferon: CB, drug combination  
 consensus interferon: DT, drug therapy  
 proteinase inhibitor: DV, drug development  
 proteinase inhibitor: DT, drug therapy  
 proteinase inhibitor: PD, pharmacology  
 thiadiazine derivative: AN, drug analysis  
 thiadiazine derivative: DV, drug development  
 thiadiazine derivative: DT, drug therapy  
 thiadiazine derivative: PD, pharmacology  
 ribamidine: DV, drug development  
 ribamidine: DT, drug therapy  
 ribamidine: TO, drug toxicity  
 ribamidine: PK, pharmacokinetics  
 ribamidine: PD, pharmacology  
 cytokine: EC, endogenous compound  
 interleukin 2: EC, endogenous compound  
 tumor necrosis factor alpha: EC, endogenous compound  
 hemoglobin: EC, endogenous compound  
 thymosin alpha1: AE, adverse drug reaction  
 thymosin alpha1: CB, drug combination  
 thymosin alpha1: DV, drug development  
 thymosin alpha1: DT, drug therapy  
 thymosin alpha1: PD, pharmacology  
 thymosin alpha1: SC, subcutaneous drug administration  
 interleukin 4: EC, endogenous compound  
 major histocompatibility antigen class 1: EC, endogenous compound  
 alpha interferon derivative: AE, adverse drug reaction  
 alpha interferon derivative: DV, drug development  
 alpha interferon derivative: DT, drug therapy  
 alpha interferon derivative: PK, pharmacokinetics  
 alpha interferon derivative: PD, pharmacology  
 albuferon: AE, adverse drug reaction  
 albuferon: DV, drug development  
 albuferon: DT, drug therapy  
 albuferon: PK, pharmacokinetics  
 albuferon: PD, pharmacology  
 unindexed drug  
 unclassified drug

CN (1) Biln 2061; (2) Nm 283; (3) Albuferon; Roferon a; Ro 25 3036;  
 Nm 107

L43 ANSWER 4 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2003195244 EMBASE  
 TITLE: Hepatitis C virus therapies: Current treatments, targets  
 and future perspectives.  
 AUTHOR: Walker M.P.; Appleby T.C.; Zhong W.; Lau J.Y.N.; Hong Z.  
 CORPORATE SOURCE: Z. Hong, Ribapharm Inc., Hyland Avenue, Costa Mesa, CA,  
 United States. zhihong@ribapharm.com  
 SOURCE: Antiviral Chemistry and Chemotherapy, (2003) 14/1 (1-21).  
 Refs: 208  
 ISSN: 0956-3202 CODEN: ACCHEH  
 COUNTRY: United Kingdom  
 DOCUMENT TYPE: Journal; General Review  
 FILE SEGMENT: 004 Microbiology  
 030 Pharmacology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Chronic hepatitis C virus (HCV) infection is the cause of an emerging global epidemic of chronic liver disease. Current combination therapies are at best 80% efficacious and are often poorly tolerated. Strategies to improve the therapeutic response include the development of novel interferons, nucleoside analogues with reduced haemolysis compared with ribavirin and inosine 5'-monophosphate dehydrogenase inhibitors. Compounds in preclinical or early clinical trials include small molecules that inhibit virus-specific enzymes (such as the serine proteases, RNA polymerase and helicase) or interfere with translation (including antisense molecules, iRNA and ribozymes). Advances in understanding HCV replication, obtaining a sub-genomic replicon and contriving potential small animal models, in addition to solving **crystallographic** structures for the replication enzymes, have improved prospects for developing novel therapies. This review summarizes current and evolving treatments for chronic hepatitis C infection. In addition, progress in HCV targets and drug discovery tools valuable in the search for novel anti-HCV agents is detailed.

AB Chronic hepatitis C virus (HCV) infection is the cause of an emerging global epidemic of chronic liver disease. Current combination therapies are at best 80% efficacious and are often poorly tolerated. Strategies to improve the therapeutic response include the development of novel interferons, nucleoside analogues with reduced haemolysis compared with ribavirin and inosine 5'-monophosphate dehydrogenase inhibitors. Compounds in preclinical or early clinical trials include small molecules that inhibit virus-specific enzymes (such as the serine proteases, RNA polymerase and helicase) or interfere with translation (including antisense molecules, iRNA and ribozymes). Advances in understanding HCV replication, obtaining a sub-genomic replicon and contriving potential small animal models, in addition to solving **crystallographic** structures for the replication enzymes, have improved prospects for developing novel therapies. This review summarizes current and evolving treatments for chronic hepatitis C infection. In addition, progress in HCV targets and drug discovery tools valuable in the search for novel anti-HCV agents is detailed.

CT Medical Descriptors:  
 \*hepatitis C: DT, drug therapy  
 \*hepatitis C: EP, epidemiology  
 \*hepatitis C: ET, etiology  
 \*chronic liver disease: ET, etiology  
 drug efficacy  
 drug tolerance  
 hemolytic anemia: SI, side effect  
 side effect: SI, side effect  
 alanine aminotransferase blood level  
 virus replication  
 replicon  
     **crystal structure**  
 RNA translation  
 untranslated region  
 internal ribosome entry site  
 monotherapy  
 virus load  
 treatment outcome  
 treatment indication  
 immunomodulation  
 drug safety  
 treatment failure  
 chimpanzee

transgenic mouse  
Hepatitis GB virus B  
IC 50  
structure activity relation  
drug structure  
virus assembly  
human  
nonhuman  
clinical trial  
review

priority journal  
Drug Descriptors:

- \*antivirus agent: AE, adverse drug reaction
- \*antivirus agent: CT, clinical trial
- \*antivirus agent: AN, drug analysis
- \*antivirus agent: CB, drug combination
- \*antivirus agent: CM, drug comparison
- \*antivirus agent: DV, drug development
- \*antivirus agent: DO, drug dose
- \*antivirus agent: DT, drug therapy
- \*antivirus agent: PD, pharmacology
- \*antivirus agent: IV, intravenous drug administration
- \*antivirus agent: SC, subcutaneous drug administration
- alpha interferon: AE, adverse drug reaction
- alpha interferon: CB, drug combination
- alpha interferon: CM, drug comparison
- alpha interferon: DO, drug dose
- alpha interferon: DT, drug therapy
- alpha interferon: PD, pharmacology
- nucleoside derivative: AN, drug analysis
- nucleoside derivative: CM, drug comparison
- nucleoside derivative: DV, drug development
- nucleoside derivative: PR, pharmaceuticals
- nucleoside derivative: PD, pharmacology
- ribavirin: AE, adverse drug reaction
- ribavirin: CT, clinical trial
- ribavirin: CB, drug combination
- ribavirin: CM, drug comparison
- ribavirin: DO, drug dose
- ribavirin: DT, drug therapy
- ribavirin: PD, pharmacology
- inosinate dehydrogenase inhibitor: CM, drug comparison
- inosinate dehydrogenase inhibitor: DT, drug therapy
- inosinate dehydrogenase inhibitor: PD, pharmacology
- serine proteinase: EC, endogenous compound
- RNA polymerase: EC, endogenous compound
- helicase: EC, endogenous compound
- ribozyme: EC, endogenous compound
- recombinant alpha2a interferon: CM, drug comparison
- recombinant alpha2a interferon: DO, drug dose
- recombinant alpha2a interferon: DT, drug therapy
- recombinant alpha2a interferon: PD, pharmacology
- recombinant alpha2a interferon: SC, subcutaneous drug administration
- recombinant alpha2b interferon: CM, drug comparison
- recombinant alpha2b interferon: DO, drug dose
- recombinant alpha2b interferon: DT, drug therapy
- recombinant alpha2b interferon: PD, pharmacology
- recombinant alpha2b interferon: SC, subcutaneous drug administration
- consensus interferon: CM, drug comparison
- consensus interferon: DO, drug dose

consensus interferon: DT, drug therapy  
consensus interferon: PD, pharmacology  
consensus interferon: SC, subcutaneous drug administration  
peginterferon alpha2b: CT, clinical trial  
peginterferon alpha2b: CB, drug combination  
peginterferon alpha2b: CM, drug comparison  
peginterferon alpha2b: DO, drug dose  
peginterferon alpha2b: DT, drug therapy  
peginterferon alpha2b: PD, pharmacology  
peginterferon alpha2a: CT, clinical trial  
peginterferon alpha2a: CB, drug combination  
peginterferon alpha2a: CM, drug comparison  
peginterferon alpha2a: DO, drug dose  
peginterferon alpha2a: DT, drug therapy  
peginterferon alpha2a: PD, pharmacology  
levovirin: CT, clinical trial  
levovirin: AN, drug analysis  
levovirin: CM, drug comparison  
levovirin: DV, drug development  
levovirin: DO, drug dose  
levovirin: DT, drug therapy  
levovirin: PD, pharmacology  
viramidine: CT, clinical trial  
viramidine: AN, drug analysis  
viramidine: CM, drug comparison  
viramidine: DV, drug development  
viramidine: DO, drug dose  
viramidine: DT, drug therapy  
viramidine: PD, pharmacology  
merimepodib: CT, clinical trial  
merimepodib: AN, drug analysis  
merimepodib: CB, drug combination  
merimepodib: CM, drug comparison  
merimepodib: DV, drug development  
merimepodib: DT, drug therapy  
merimepodib: PD, pharmacology  
thymosin alpha1: CT, clinical trial  
thymosin alpha1: AN, drug analysis  
thymosin alpha1: CB, drug combination  
thymosin alpha1: DV, drug development  
thymosin alpha1: DO, drug dose  
thymosin alpha1: DT, drug therapy  
thymosin alpha1: PD, pharmacology  
thymosin alpha1: SC, subcutaneous drug administration  
amantadine: CT, clinical trial  
amantadine: AN, drug analysis  
amantadine: CB, drug combination  
amantadine: CM, drug comparison  
amantadine: DV, drug development  
amantadine: PD, pharmacology  
recombinant interleukin 12: CT, clinical trial  
recombinant interleukin 12: AN, drug analysis  
recombinant interleukin 12: CB, drug combination  
recombinant interleukin 12: CM, drug comparison  
recombinant interleukin 12: DV, drug development  
recombinant interleukin 12: DO, drug dose  
recombinant interleukin 12: DT, drug therapy  
recombinant interleukin 12: PD, pharmacology  
histamine: CT, clinical trial  
histamine: AN, drug analysis

histamine: CB, drug combination  
 histamine: DV, drug development  
 histamine: DT, drug therapy  
 histamine: PD, pharmacology  
 gamma interferon: CT, clinical trial  
 gamma interferon: AN, drug analysis  
 gamma interferon: CB, drug combination  
 gamma interferon: DV, drug development  
 gamma interferon: DT, drug therapy  
 gamma interferon: PD, pharmacology  
 proteinase inhibitor: CT, clinical trial  
 proteinase inhibitor: DO, drug dose  
 proteinase inhibitor: PD, pharmacology  
 proteinase inhibitor: PO, oral drug administration

**biln 2061: CT, clinical trial**

**biln 2061: DO, drug dose**

**biln 2061: PD, pharmacology**

**biln 2061: PO, oral drug administration**

peptide derivative: AN, drug analysis  
 peptide derivative: DV, drug development  
 peptide derivative: PD, pharmacology  
 peptide alpha keto acid: AN, drug analysis  
 peptide alpha keto acid: DV, drug development  
 peptide alpha keto acid: PD, pharmacology  
 pyrrolidine derivative: AN, drug analysis  
 pyrrolidine derivative: DV, drug development  
 pyrrolidine derivative: PD, pharmacology  
 pyrrolidine 5,5 lactam: AN, drug analysis  
 pyrrolidine 5,5 lactam: DV, drug development  
 pyrrolidine 5,5 lactam: PD, pharmacology  
 IDdb3: DV, drug development  
 IDdb3: PD, pharmacology  
 unindexed drug  
 unclassified drug  
 isis 14803

gw 3112

gw 2549

gw 0569

n [4 [[[6,7 dihydro 2 (4 methylphenyl) 5h benzocyclohepten 8

yl]carbonyl]amino]benzyl] n,n dimethyl 2h tetrahydropyran 4 aminium  
 chloride

1,1' [1,4 phenylenebis(methylene)]bis(1,4,8,11 tetraazacyclotetradecane)

CN (1) Vx 497; (2) Ceplene; (3) **Biln 2061**; (4) Isis 14803; Zadaxin;

Gw 3112; Gw 2549; Gw 0569; Tak 779; Amd 3100; IDdb3

=>.FIL STNGUIDE

FILE 'STNGUIDE' ENTERED AT 12:32:47 ON 13 OCT 2004  
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 COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE  
 AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.  
 LAST RELOADED: Oct 8, 2004 (20041008/UP).

=>

(FILE 'CONFSCI, MEDICONF, PASCAL, CABA' ENTERED AT 12:35:08 ON 13 OCT  
 2004)

=> d que 146

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L6      1 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/RN
L7      0 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/CRN
L8      1 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L6 OR L7)
L44     SEL  PLU=ON  L8 1-  CHEM :      4 TERMS
L45     4 SEA L44
L46     4 DUP REM L45 (0 DUPLICATES REMOVED)

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=> d ibib abs 146 1-

YOU HAVE REQUESTED DATA FROM FILE 'PASCAL' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 4 ANSWERS - CONTINUE? Y/(N):y

L46 ANSWER 1 OF 4 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

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ACCESSION NUMBER:      2004-0392927  PASCAL
COPYRIGHT NOTICE:     Copyright .COPYRGT. 2004 INIST-CNRS. All rights
                        reserved.
TITLE (IN ENGLISH):    Sensitivity of NS3 serine proteases from hepatitis C
                        virus genotypes 2 and 3 to the inhibitor BILN
                        2061
AUTHOR:                THIBEAULT Diane; BOUSQUET Christiane; GINGRAS Rock;
                        LAGACE Lisette; MAURICE Roger; WHITE Peter W.; LAMARRE
                        Daniel
CORPORATE SOURCE:       Department of Biological Sciences, Boehringer
                        Ingelheim (Canada) Ltd., Research and Development,
                        Laval, Quebec H7S 2G5, Canada
SOURCE:                Journal of virology, (2004), 78(14), 7352-7359, 33
                        refs.
                        ISSN: 0022-538X
DOCUMENT TYPE:          Journal
BIBLIOGRAPHIC LEVEL:    Analytic
COUNTRY:                United States
LANGUAGE:               English
AVAILABILITY:           INIST-13592, 354000113683220070

```

AN 2004-0392927 PASCAL

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AB Hepatitis C virus (HCV) displays a high degree of genetic variability. Six genotypes and more than 50 subtypes have been identified to date. In this report, kinetic profiles were determined for NS3 proteases of genotypes 1a, 1b, 2ac, 2b, and 3a, revealing no major differences in activity. In vitro sensitivity studies with **BILN 2061** showed a decrease in affinity for proteases of genotypes 2 and 3 (K.sub.i, 80 to 90 nM) compared to genotype 1 enzymes (K.sub.i, 1.5 nM). To understand the reduced sensitivity of genotypes 2 and 3 to **BILN 2061**, active-site residues in the proximity of the inhibitor binding site were replaced in the genotype-1b enzyme with the corresponding genotype-2b or -3a residues. The replacement of five residues at positions 78, 79, 80, 122, and 132 accounted for most of the reduced sensitivity of genotype 2b, while replacement of residue 168 alone could account for the reduced sensitivity of genotype 3a. **BILN 2061** remains a potent inhibitor of these non-genotype-1 NS3-NS4A proteins, with K.sub.i values below 100 nM. This in vitro potency, in conjunction with the good pharmacokinetic data reported for humans, suggests that there is potential for **BILN 2061** as an antiviral agent for individuals infected with

non-genotype-1 HCV.

L46 ANSWER 2 OF 4 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004-0323488 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Mutations conferring resistance to a potent hepatitis C virus serine protease inhibitor in vitro  
 AUTHOR: LU Liangjun; PILOT-MATIAS Tami J.; STEWART Kent D.; RANDOLPH John T.; PITHAWALLA Ron; WENPING HE; HUANG Peggy P.; KLEIN Larry L.; MO Hongmei; MOLLA Akhteruzzaman  
 CORPORATE SOURCE: Antiviral Research,, Abbott Laboratories, Global Pharmaceutical Research and Development, Abbott Park, Illinois, United States; Structural Biology, Abbott Laboratories; Global Pharmaceutical Research and Development, Abbott Park, Illinois, United States  
 SOURCE: Antimicrobial agents and chemotherapy, (2004), 48(6), 2260-2266, 32 refs.  
 ISSN: 0066-4804 CODEN: AACHAX  
 DOCUMENT TYPE: Journal  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: United States  
 LANGUAGE: English  
 AVAILABILITY: INIST-13334, 354000112018870510

AN 2004-0323488 PASCAL  
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 AB **BILN 2061** is a novel, specific hepatitis C virus (HCV) NS3 serine protease inhibitor discovered by Boehringer Ingelheim that has shown potent activity against HCV replicons in tissue culture and is currently under clinical investigation for the treatment of HCV infection. The poor fidelity of the HCV RNA-dependent RNA polymerase will likely lead to the development of drug-resistant viruses in treated patients. The development of resistance to **BILN 2061** was studied by the in vitro passage of HCV genotype 1b replicon cells in the presence of a fixed concentration of the drug. Three weeks posttreatment, four colonies were expanded for genotypic and phenotypic characterization. The 50% inhibitory concentrations of **BILN 2061** for these colonies were 72- to 1,228-fold higher than that for the wild-type replicon. Sequencing of the individual colonies identified several mutations in the NS3 serine protease gene. Molecular clones containing the single amino acid substitution A156T, R155Q, or D168V resulted in 357-fold, 24-fold, and 144-fold reductions in susceptibility to **BILN 2061**, respectively, compared to the level of susceptibility shown by the wild-type replicon. Modeling studies indicate that all three of these residues are located in close proximity to the inhibitor binding site. These findings, in addition to the three-dimensional structure analysis of the NS3/NS4A serine protease inhibitor complex, provide a strategic guide for the development of next-generation inhibitors of HCV NS3/NS4A serine protease.

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ACCESSION NUMBER: 2004-0488805 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): Structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN**

2061

AUTHOR: LLINAS-BRUNET Montse; BAILEY Murray D.; BOLGER Gordon; BROCHU Christian; FAUCHER Anne-Marie; FERLAND Jean Marie; GARNEAU Michel; GHIRO Elise; GORYS Vida; GRAND-MAITRE Chantal; HALMOS Ted; LAPEYRE-PAQUETTE Nicole; LIARD Francine; POIRIER Martin; RHEAUME Manon; TSANTRIZOS Youla S.; LAMARRE Daniel

CORPORATE SOURCE: Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., 2100 Cunard Street, Laval, Quebec H7S 2G5, Canada; Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd., 2100 Cunard Street, Laval, Quebec H7S 2G5, Canada

SOURCE: Journal of medicinal chemistry : (Print), (2004), 47(7), 1605-1608  
ISSN: 0022-2623 CODEN: JMCMAR

DOCUMENT TYPE: Journal; Letter

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United States

LANGUAGE: English

NOTE: 3/4 p. ref. et notes

AVAILABILITY: INIST-9165, 354000113547020040

AN 2004-0488805 PASCAL

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AB From the discovery of competitive hexapeptide inhibitors, potent and selective HCV NS3 protease macrocyclic inhibitors have been identified. Structure-activity relationship studies were performed focusing on optimizing the N-terminal carbamate and the aromatic substituent on the (4R)-hydroxyproline moiety. Inhibitors meeting the potency criteria in the cell-based assay and with improved oral bioavailability in rats were identified. **BILN 2061** was selected as the best compound, the first NS3 protease inhibitor reported with antiviral activity in man.

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ACCESSION NUMBER: 2004-0112784 PASCAL

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TITLE (IN ENGLISH): An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus

AUTHOR: LAMARRE Daniel; ANDERSON Paul C.; BAILEY Murray; BEAULIEU Pierre; BOLGER Cordon; BONNEAU Pierre; BOES Michael; CAMERON Dale R.; CARTIER Mireille; CORDINGLEY Michael G.; FAUCHER Anne-Marie; GOUDREAU Nathalie; KAWAL Stephen H.; KUKOLJ George; LAGACE Lisette; LAPLANTE Steven R.; NARJES Hans; POUPART Marc-Andre; RANCOURT Jean; SENTJENS Roel E.; GEORGE Roger St.; SIMONEAU Bruno; STEINMANN Gerhard; THIBEAULT Diane; TSANTRIZOS Youla S.; WELDON Steven M.; YONG Chan-Lol; LLINAS-BRUNET Montse

CORPORATE SOURCE: Departments of Biological Sciences, Laval, Quebec, H7S 2G5, Canada; Chemistry, Research and Development, Boehringer Ingelheim (Canada) Ltd, Laval, Quebec, H7S 2G5, Canada; Clinical Research, Boehringer Ingelheim Pharma KG, Biberach 88397, Germany, Federal Republic of; Academisch Medisch Center, 1105 AZ, Amsterdam, Netherlands; Research and Development, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut 06877-0368, United States

SOURCE: Nature : (London), (2003), 426(6963), 186-189, 30

refs.  
 ISSN: 0028-0836 CODEN: NATUAS  
 DOCUMENT TYPE: Journal; (letter to editor)  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: United Kingdom  
 LANGUAGE: English  
 AVAILABILITY: INIST-142, 354000119799120240  
 AN 2004-0112784 PASCAL  
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 AB Hepatitis C virus (HCV) infection is a serious cause of chronic liver disease worldwide with more than 170 million infected individuals at risk of developing significant morbidity and mortality.<sup>1</sup><sup>2</sup><sup>3</sup>. Current interferon-based therapies.<sup>4</sup> are suboptimal especially in patients infected with HCV genotype 1, and they are poorly tolerated, highlighting the unmet medical need for new therapeutics.<sup>5</sup><sup>6</sup>. The HCV-encoded NS3 protease is essential for viral replication.<sup>7</sup><sup>8</sup> and has long been considered an attractive target for therapeutic intervention in HCV-infected patients. Here we identify a class of specific and potent NS3 protease inhibitors and report the evaluation of **BILN 2061**, a small molecule inhibitor biologically available through oral ingestion and the first of its class in human trials. Administration of **BILN 2061** to patients infected with HCV genotype 1 for 2 days resulted in an impressive reduction of HCV RNA plasma levels, and established proof-of-concept in humans for an HCV NS3 protease inhibitor. Our results further illustrate the potential of the viral-enzyme-targeted drug discovery approach for the development of new HCV therapeutics.

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 FILE 'ENCOMPLIT2' ACCESS NOT AUTHORIZED  
 FILE 'ENCOMPPAT' ACCESS NOT AUTHORIZED  
 FILE 'ENCOMPPAT2' ACCESS NOT AUTHORIZED

INDEX 'IMOBILITY, 2MOBILITY, ABI-INFORM, ADISCTI, AEROSPACE, AGRICOLA, ALUMINIUM, ANABSTR, ANTE, APOLLIT, AQUASCI, AQUALINE, AQUIRE, BABS, BIBLIODATA, BIOBUSINESS, BIOCOMMERCE, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, BLLDB, CABA, CANCERLIT, ...'  
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143 FILES IN THE FILE LIST IN STNINDEX

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=> s (?ciluprevir? or (biln 2061?) or (biln(1w)2061?)) and ?cryst?

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L47 QUE (?CILUPREVIR? OR (BILN 2061?) OR (BILN(1W) 2061?)) AND ?CRYST?

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F4 3 BIOTECHNO  
F5 3 SCISEARCH  
F6 1\* INVESTEXT

=> fil biotechno scisearch

=> =>

(FILE 'BIOTECHNO, SCISEARCH' ENTERED AT 12:45:07 ON 13 OCT 2004)

=> d que l51

L6 1 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/RN  
L7 0 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/CRN  
L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON (L6 OR L7)  
L48 SEL PLU=ON L8 1- CHEM : 4 TERMS  
L49 32 SEA L48  
L50 30 DUP REM L49 (2 DUPLICATES REMOVED)  
L51 3 SEA L50 (L) ?CRYST?

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L51 ANSWER 1 OF 3 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN  
ACCESSION NUMBER: 2003:37413258 BIOTECHNO  
TITLE: Current therapy and new molecular approaches to  
antiviral treatment and prevention of hepatitis C  
AUTHOR: Hugle T.; Cerny A.  
CORPORATE SOURCE: Dr. A. Cerny, Clinica Medica, Ospedale Civico, CH-6903  
Lugano, Switzerland.  
E-mail: andreas.cerny@bluewin.ch  
SOURCE: Reviews in Medical Virology, (2003), 13/6 (361-371),  
79 reference(s)  
CODEN: RMVIEW ISSN: 1052-9276  
DOCUMENT TYPE: Journal; General Review  
COUNTRY: United Kingdom  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
AN 2003:37413258 BIOTECHNO  
AB Current therapeutic options for hepatitis C are limited, especially for  
genotype 1. For genotypes 2 and 3, pegylated interferon in combination  
with ribavirin, can lead to a sustained virological response in up to 80%  
of patients. Unfortunately, adverse effects of IFN and ribavirin are a  
major problem and the list of contraindications for HCV therapy is long,  
including decompensated cirrhosis of the liver and psychiatric disorders.  
Therefore, alternative therapeutic approaches are needed. New delivery  
options for IFN and ribavirin are aimed at optimising efficiency and  
reducing adverse effects. Recent progress in the molecular virology of  
HCV has identified new targets for antiviral intervention. Inhibition of  
HCV gene expression and replication as well as immunotherapeutic concepts  
aimed at enhancing the cellular immune response against HCV are being  
explored. Solution of the crystal structures of HCV key enzymes led to  
the design of specific inhibitors including compounds active against the  
well characterised NS3 serine protease and RNA-dependent RNA polymerase  
which are currently in the early phase clinical investigation. New  
strategies for inhibiting HCV gene expression include the use of

antisense oligodeoxynucleotides and ribozymes. Immunomodulation by agents such as inosine monophosphate dehydrogenase inhibitors, thymosin-alpha 1, histamine or amantadine are being studied in combination with IFN and/or ribavirin. Immunotherapeutic vaccination with recombinant HCV E1 protein improved host immunity against HCV and thus seems to be a promising new option. Copyright .COPYRGT. 2003 John Wiley & Sons, Ltd.

L51 ANSWER 2 OF 3 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN  
ACCESSION NUMBER: 2003:36949689 BIOTECHNO  
TITLE: Promising candidates for the treatment of chronic hepatitis C  
AUTHOR: Walker M.P.; Yao N.; Hong Z.  
CORPORATE SOURCE: Z. Hong, Drug Discovery, Ribapharm Inc., 3300 Hyland Avenue, Costa Mesa, CA 92626, United States.  
SOURCE: Expert Opinion on Investigational Drugs, (01 AUG 2003), 12/8 (1269-1280), 113 reference(s)  
CODEN: EOIDER ISSN: 1354-3784  
DOCUMENT TYPE: Journal; General Review  
COUNTRY: United Kingdom  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
AN 2003:36949689 BIOTECHNO  
AB Chronic hepatitis C virus (HCV) infection is the cause of an emerging global pandemic of chronic liver disease. Current pegylated IFN- $\alpha$ /ribavirin combination therapies are merely 54 - 56% efficacious and are often poorly tolerated. Popular strategies to improve upon existing therapies include efforts to decrease the dosing regime, improve the safety profile and specifically target the liver, the site of HCV replication. A clear goal of novel therapies is to significantly improve the therapeutic response for HCV-infected patients. One popular scheme to accomplish this is to directly target the viral enzymes involved in HCV RNA replication. While peptidomimetics have been pursued as potent and specific inhibitors of the serine protease, nucleoside analogues and non-nucleoside small molecules have been explored as RNA-dependent RNA polymerase inhibitors with promising potential. Advances in the understanding of HCV replication at the molecular level that stem from the use of the subgenomic replicon system, in vitro enzyme assays and from co-crystallographic structure solutions of the replication enzymes with novel inhibitors have propelled these compounds into clinical development. As these candidates are developed further, there is great hope for a cure for all those chronically infected with HCV.

L51 ANSWER 3 OF 3 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN  
ACCESSION NUMBER: 2003:36565908 BIOTECHNO  
TITLE: Hepatitis C virus therapies: Current treatments, targets and future perspectives  
AUTHOR: Walker M.P.; Appleby T.C.; Zhong W.; Lau J.Y.N.; Hong Z.  
CORPORATE SOURCE: Z. Hong, Ribapharm Inc., Hyland Avenue, Costa Mesa, CA, United States.  
E-mail: zhihong@ribapharm.com  
SOURCE: Antiviral Chemistry and Chemotherapy, (2003), 14/1 (1-21), 208 reference(s)  
CODEN: ACCHEH ISSN: 0956-3202  
DOCUMENT TYPE: Journal; General Review  
COUNTRY: United Kingdom  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
AN 2003:36565908 BIOTECHNO

AB Chronic hepatitis C virus (HCV) infection is the cause of an emerging global epidemic of chronic liver disease. Current combination therapies are at best 80% efficacious and are often poorly tolerated. Strategies to improve the therapeutic response include the development of novel interferons, nucleoside analogues with reduced haemolysis compared with ribavirin and inosine 5'-monophosphate dehydrogenase inhibitors. Compounds in preclinical or early clinical trials include small molecules that inhibit virus-specific enzymes (such as the serine proteases, RNA polymerase and helicase) or interfere with translation (including antisense molecules, iRNA and ribozymes). Advances in understanding HCV replication, obtaining a sub-genomic replicon and contriving potential small animal models, in addition to solving crystallographic structures for the replication enzymes, have improved prospects for developing novel therapies. This review summarizes current and evolving treatments for chronic hepatitis C infection. In addition, progress in HCV targets and drug discovery tools valuable in the search for novel anti-HCV agents is detailed.

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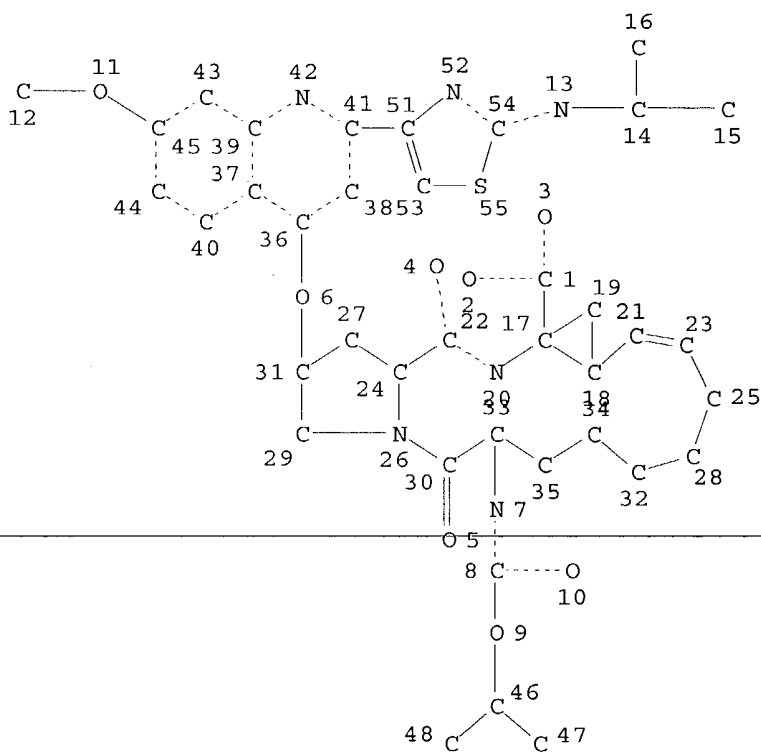
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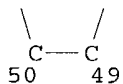
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L52

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Page 2-A

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10/13/2004

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MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the  
MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and  
[http://www.nlm.nih.gov/pubs/techbull/nd03/nd03\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html) for a  
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=> d que 171

L54 15 SEA ("CERRETA M K"/AU OR "CERRETA MICHAEL K"/AU OR "CERRETA  
MICHAEL KENNETH"/AU)  
L55 50 SEA ("VARSolona R J"/AU OR "VARSolona RICHARD"/AU OR "VARSolona  
RICHARD J"/AU)  
L56 1 SEA SMOLIGA,J?/AU  
L57 66 SEA (L54 OR L55 OR L56)  
L58 45 DUP REM L57 (21 DUPLICATES REMOVED)  
L59 429328 SEA HCV OR ?HEPATITI?  
L60 0 SEA L58 AND L59  
L61 159 SEA ?CILUPREVIR? OR BILN?  
L62 0 SEA L58 AND L61  
L63 30112 SEA ?BOEHRINGER?  
L64 12432 SEA ?INGELHEIM?  
L65 0 SEA L58 AND (L63 OR L64)  
L66 31742 SEA ?BOEHRINGER?/PA,CS,SO  
L67 20390 SEA ?INGELHEIM?/PA,CS,SO  
L68 1 SEA L58 AND (L66 OR L67)  
L69 24 SEA L58 AND ?CRYST?  
L70 25 SEA L60 OR L62 OR L65 OR L68 OR L69  
L71 25 SEA L70 OR L56

=> d ibib abs

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, BIOSIS, PASCAL, EMBASE' - CONTINUE?  
(Y)/N:y

L71 ANSWER 1 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN  
ACCESSION NUMBER: 2003:877280 HCAPLUS  
DOCUMENT NUMBER: 140:111069  
TITLE: Scalable, efficient process for the synthesis of  
(R)-3,5-bistrifluoromethylphenyl ethanol via catalytic  
asymmetric transfer hydrogenation and isolation as a  
DABCO inclusion complex  
AUTHOR(S): Hansen, Karl B.; Chilenski, Jennifer R.; Desmond,  
Richard; Devine, Paul N.; Grabowski, Edward J. J.;  
Heid, Richard; Kubryk, Michele; Mathre, David J.;  
**Varsolona, Richard**  
CORPORATE SOURCE: Merck Research Laboratories, Department of Process

SOURCE: Research, Rahway, NJ, 07065, USA  
Tetrahedron: Asymmetry (2003), 14(22), 3581-3587  
CODEN: TASYE3; ISSN: 0957-4166  
PUBLISHER: Elsevier Science B.V.  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
OTHER SOURCE(S): CASREACT 140:111069  
AB (R)-3,5-Bistrifluoromethylphenyl ethanol (I), a key building block in the synthesis of aprepitant, has been synthesized from corresponding ketone via catalytic asym. transfer hydrogenation using a simplified catalyst generation procedure. The process uses (1S,2R)-cis-1-aminoindan-2-ol and dichloro(p-cymene)Ru(II)dimer as the chiral ligand and metal source for the reduction. While the reduction provides I in 90-92% ee, an isolation of I as a 2:1 inclusion complex with DABCO was developed to allow for the upgrade of the enantiomeric excess to >99%. **Crystal** structure of this complex was also reported.  
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs 2-

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, BIOSIS, PASCAL, EMBASE' - CONTINUE?  
(Y)/N:y

YOU HAVE REQUESTED DATA FROM 24 ANSWERS - CONTINUE? Y/(N):y

L71 ANSWER 2 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:902262 HCAPLUS  
DOCUMENT NUMBER: 138:4786  
TITLE: Thermodynamically stable **crystal** form of the insecticidal 4''-deoxy-4''-epi-methylamino avermectin Bla/B1b benzoic acid salt, and processes for its preparation  
INVENTOR(S): Cvetovich, Raymond; McCauley, James A.; Demchak, Richard; **Varsolona, Richard J.**  
PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
SOURCE: U.S., 4 pp., Cont.-in-part of U.S. Ser. No. 109,189, abandoned.  
CODEN: USXXAM  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 3  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6486195	B1	20021126	US 1995-376318	19950120
CN 1129453	A	19960821	CN 1994-193136	19940815
CN 1041523	B	19990106		
HU 73552	A2	19960828	HU 1996-345	19940815
HU 217769	B	20000428		
BR 9407300	A	19961008	BR 1994-7300	19940815
ES 2139753	T3	20000216	ES 1994-926502	19940815
PT 714400	T	20000531	PT 1994-926502	19940815
CZ 287929	B6	20010314	CZ 1996-459	19940815
ZA 9406203	A	19950331	ZA 1994-6203	19940817
WO 9622300	A1	19960725	WO 1996-US459	19960116

W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS,

JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL,  
RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AZ, BY, KG,  
KZ, RU

RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR,  
NE, SN, TD, TG

AU 9646990	A1	19960807	AU 1996-46990	19960116
LV 12571	B	20010420	LV 2000-120	20000907
PRIORITY APPLN. INFO.:			US 1993-109189	B2 19930819
			US 1995-376318	A 19950120
			WO 1996-US459	W 19960116

OTHER SOURCE(S): CASREACT 138:4786

AB The most thermodynamically stable **crystalline** form of the insecticidal benzoic acid salt of 4''-deoxy-4''-epi-methylamino avermectin B1a/B1b as the hemihydrate is obtained by **crystallization** from organic solvents containing a controlled amount of water.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L71 ANSWER 3 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:859280 HCAPLUS

DOCUMENT NUMBER: 139:312088

TITLE: A spectroscopic and **crystallographic** study of polymorphism in an aza-steroid. [Erratum to document cited in CA134:32861]

AUTHOR(S): Wenslow, Robert M.; Baum, Mary W.; Ball, Richard G.; McCauley, James A.; **Varsolona, Richard J.**

CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065-0900, USA

SOURCE: Journal of Pharmaceutical Sciences (2002), 91(11), 2465

CODEN: JPMSAE; ISSN: 0022-3549

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The solubility anal. in the exptl. section is incorrect. While the information about solubility trends and form stability are correct, the actual solubility values

are unreliable. The solubility measurements portion of the exptl. section (page 1271), Figure 3 (page 1273), and the second paragraph of the results and discussion section (page 1272) must be retracted.

L71 ANSWER 4 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:185054 HCAPLUS

DOCUMENT NUMBER: 136:232164

TITLE: Preparation of the dihydroxy open-acid salt of simvastatin as a HMG-CoA reductase inhibitor for pharmaceutical use in the treatment of conditions, such as hypercholesteremia and atherosclerosis

INVENTOR(S): Tillyer, Richard D.; Reider, Paul J.; Grabaowski, Edward J. J.; Xu, Feng; Wenslow, Robert M.; Vega, Jose M.; **Varsolona, Richard J.**

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 106 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002020457	A1	20020314	WO 2001-US27466	20010905
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001088724	A5	20020322	AU 2001-88724	20010905
EP 1324972	A1	20030709	EP 2001-968480	20010905
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004508347	T2	20040318	JP 2002-525082	20010905
US 2003176501	A1	20030918	US 2002-293153	20021113
PRIORITY APPLN. INFO.: US 2000-656109 A 20000906 US 2000-660956 A1 20000913 WO 2001-US27466 W 20010905				
<b>AB Crystalline</b> forms of open chain simvastatin were prepared for use in pharmaceutical comps. for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, comprising orally administering a therapeutically effective amount of a <b>crystalline</b> hydrated form of the calcium salt of dihydroxy open acid simvastatin to a patient in need of such treatment. Thus, simvastatin was treated with Ca(OAc) <sub>2</sub> and 1N HCl to form open-chain simvastatin acid calcium salt. Pharmacokinetics and HMG-CoA reductase inhibiting activity of the prepared simvastatin derivs. were examined				
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT				

L71 ANSWER 5 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

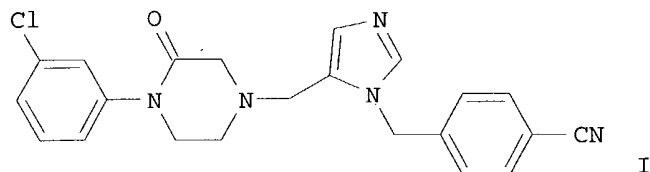
ACCESSION NUMBER: 2001:78384 HCAPLUS  
 DOCUMENT NUMBER: 134:136678  
 TITLE: **Crystal** forms of 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone  
 INVENTOR(S): Varsolona, Richard J.; McCauley, James A.  
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
 SOURCE: PCT Int. Appl., 43 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007437	A1	20010201	WO 2000-US19423	20000717
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:  
GI

US 1999-144954P

P 19990721



AB The present invention is directed to the **crystal** forms of 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone (I), which may inhibit farnesyl-protein transferase, and the process for the preparation of these **crystal** forms. The hydrate and 2 other **crystal** forms of I were prepared and pharmaceutical formulations given.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L71 ANSWER 6 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:737606 HCAPLUS

DOCUMENT NUMBER: 134:32861

TITLE: A spectroscopic and **crystallographic** study of polymorphism in an aza-steroid

AUTHOR(S): Wenslow, Robert M.; Baum, Mary W.; Ball, Richard G.; Mccauley, James A.; Varsolona, Richard J.

CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065-0900, USA

SOURCE: Journal of Pharmaceutical Sciences (2000), 89(10), 1271-1285

CODEN: JPMSAE; ISSN: 0022-3549

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The **crystal** structures of 2 enantiotropic polymorphs of the aza-steroid, finasteride, were determined. The solid-state NMR spectra, IR spectra, and phys. property data of these 2 polymorphs are discussed in relation to both their solid-state structures and hydrogen-bonding networks.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L71 ANSWER 7 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:335413 HCAPLUS

DOCUMENT NUMBER: 132:339389

TITLE: Therapeutic polymorphs of a GABA-A  $\alpha$ -5 inverse agonist and pamoate formulations

INVENTOR(S): Kaufman, Michael J.; Mccauley, James A.; Rush, Daniel J.; Tschaen, David M.; Varsolona, Richard J.; Ho, Guo-Jie

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 29 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000027849	A2	20000518	WO 1999-US26622	19991110
WO 2000027849	A3	20000831		
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1129094	A2	20010905	EP 1999-961637	19991110
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
JP 2002529468	T2	20020910	JP 2000-581027	19991110
US 2001049439	A1	20011206	US 2000-728497	20001130
US 6534505	B2	20030318		
PRIORITY APPLN. INFO.:			US 1998-108007P	P 19981112
			US 1999-437928	A3 19991110
			WO 1999-US26622	W 19991110
AB	Pharmaceutical compns. containing 3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl)methoxy-1,2,4-triazolo[3,4-a]phthalazine (I) as a dihydrate, a dehydrate of the dihydrate and a pentahydrate for enhancing cognition, and pamoate are described. I dihydrate (0.99 g) was dry mixed with disodium pamoate (3.6 g), HPC-LF (0.225 g) and Avicel PH-102 (1.155 g) until a uniform mixture was obtained. Small amts. of water (1.75 g) were added and mixed into the powder until granules were obtained. The granules were sieved and permitted to air dry for 7 days. Dried granules (2.43 g) were mixed with PVP (0.0972 g) for 2 min. Ten tablets (nominal weight 208 mg) were compressed from the granulate. The tablets were introduced to 900 g placebo tablets and warmed to 40°, after which a 15% Surerelease dispersion in water was applied until a 10% weight gain was achieved. The resulting enteric coated tablets were stored at RT for future use.			

L71 ANSWER 8 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 1998:709087 HCAPLUS  
 DOCUMENT NUMBER: 129:290373  
 TITLE: Flowable, nondigestible oil and manufacturing process  
 INVENTOR(S): Cerreta, Michael Kenneth; Lin, Peter  
 Yau-Tak; Edwards, Penelope Marie; Agerton, Mark Lewis  
 PATENT ASSIGNEE(S): The Procter & Gamble Company, USA  
 SOURCE: PCT Int. Appl., 48 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9847909	A1	19981029	WO 1998-US6708	19980403
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,			

NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,  
 UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,  
 FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,  
 CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9872457 A1 19981113 AU 1998-72457 19980403  
 EP 977765 A1 20000209 EP 1998-919733 19980403

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI

PRIORITY APPLN. INFO.: US 1997-844590 19970421

US 1997-914743 19970819

WO 1998-US6708 19980403

AB A title oil composition having a consistency of <600 P·sec(n-1) in a temperature range of 20-40° contains a liquid polyol (preferably sucrose) polyester having a complete melt point <37° (body temperature), and a solid polyol polyester having a complete melt point of ≥37° and containing saturated polyol polyester capable of forming **crystallized** spherulites. The composition is flowable at ordinary ambient temperature and also

provides good control of passive oil loss (leakage of the liquid nondigested fat through the anal sphincter). The composition is made by melting completely the nondigestible oil containing the solid polyol fatty acid polyester, e.g., sucrose octabehenate, **crystallizing** a portion of the solid polyester into **crystallized** spherulites (cores), further reducing the temperature to an ambient **crystallization** temperature, and holding the polyol polyester composition for a time sufficient to **crystallize** the remaining portion of the solid polyol polyesters diversely esterified, e.g., with C18 (un)saturated fatty acid mixts. around the solid core. The process is accompanied by shearing of the composition during the **crystallization** of the remaining portion of the solid polyol fatty acid polyester. The process is generally completed within 5 h, usually within .apprx.2 h.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L71 ANSWER 9 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:717898 HCAPLUS

DOCUMENT NUMBER: 128:22922

TITLE: Preparation of 3-amino-2-pyrazinone-1-acetamide derivatives as thrombin inhibitors

INVENTOR(S): Sanderson, Philip E.; Lyle, Terry A.; Dorsey, Bruce D.; Varsolona, Richard J.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Sanderson, Philip E.; Lyle, Terry A.; Dorsey, Bruce D.; Varsolona, Richard J.

SOURCE: PCT Int. Appl., 193 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

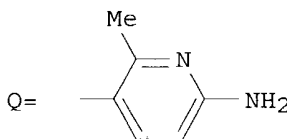
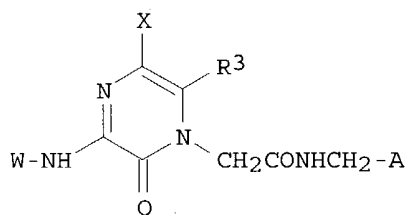
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9740024	A1	19971030	WO 1997-US6744	19970418
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2252964	AA	19971030	CA 1997-2252964	19970418

AU 9726799	A1	19971112	AU 1997-26799	19970418
AU 714985	B2	20000113		
EP 900207	A1	19990310	EP 1997-918780	19970418
EP 900207	B1	20011121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
BR 9708859	A	19990803	BR 1997-8859	19970418
NZ 331993	A	20000428	NZ 1997-331993	19970418
JP 2000508334	T2	20000704	JP 1997-538296	19970418
JP 3140790	B2	20010305		
TR 9802133	T2	20000921	TR 1998-9802133	19970418
AT 209191	E	20011215	AT 1997-918780	19970418
ZA 9703437	A	19971023	ZA 1997-3437	19970422
NO 9804928	A	19981222	NO 1998-4928	19981022
KR 2000010650	A	20000225	KR 1998-708609	19981022
PRIORITY APPLN. INFO.:			US 1996-16041P	P 19960423
			GB 1996-9714	A 19960509
			US 1997-43009P	P 19970414
			WO 1997-US6744	W 19970418

OTHER SOURCE(S): MARPAT 128:22922  
GI



AB Compds. of general formula [I; W = H, R<sub>1</sub>, R<sub>1</sub>O<sub>2</sub>C, R<sub>1</sub>CO, R<sub>1</sub>(CH<sub>2</sub>)<sub>n</sub>NHCO, (R<sub>1</sub>)<sub>2</sub>CH(CH<sub>2</sub>)<sub>n</sub>NHCO, wherein n = 1-4; R<sub>1</sub> = R<sub>2</sub>, R<sub>2</sub> (CH<sub>2</sub>)<sub>m</sub> C(R<sub>12</sub>)<sub>2</sub>, R<sub>2</sub>CH(OR<sub>2</sub>) (CH<sub>2</sub>)<sub>p</sub>, R<sub>2</sub>C(R<sub>12</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>m</sub>, R<sub>2</sub>CH<sub>2</sub>C(R<sub>12</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>q</sub>, (R<sub>2</sub>)<sub>2</sub>CH(CH<sub>2</sub>)<sub>r</sub>, R<sub>2</sub>O(CH<sub>2</sub>)<sub>p</sub>, R<sub>2</sub>(CO<sub>2</sub>R<sub>3</sub>)(CH<sub>2</sub>)<sub>s</sub>, etc.; wherein p, s = 1-4; m = 0-3; q = 0-2; r = 0-4; R<sub>2</sub> = (un)substituted Ph, naphthyl, biphenyl, (un)substituted and (un)saturated 5- to 7-membered mono- or 9- to 10-membered bicyclic heterocyclic ring or non-heterocyclic ring, wherein the heterocyclic ring contains 1-4 heteroatoms selected from N, O, and S; R<sub>3</sub> = H, C1-4 alkyl, C3-7 cycloalkyl, CF<sub>3</sub>; X = H, halo; ring-(un)substituted 2-amino-5-pyridyl or 2-amino-4-pyridyl, (un)substituted Ph] are prepared. These compds. are useful in inhibiting thrombin (serine protease) and associated thrombotic occlusions. This invention also includes a pharmaceutical composition containing I for inhibiting thrombus formation and a method for inhibiting thrombin in blood and formation of blood platelet aggregates by adding the composition to the blood and also a method for inhibiting thrombus formation by adding the composition to the blood and/or with a fibrinogen receptor antagonist. A method for treating or preventing venous thromboembolism and pulmonary embolism, deep vein thrombosis, cardiogenic thromboembolism, thromboembolic stroke, thrombus associated with cancer and cancer chemotherapy, unstable angina, myocardial infarction, cardiogenic thromboembolism associated with atrial fibrillation, prosthetic heart valves, or heart disease, atherosclerosis, etc. in a mammal by administering the composition is claimed. Thus, 3-(2-phenethylamino)-6-methyl-1-carboxypyridine was condensed with 2-amino-5-aminomethyl-6-methylpyridine dihydrochloride using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride,

HOBT.H<sub>2</sub>O, and N-methylmorpholine in DMF for 16 h to give I (W = CH<sub>2</sub>CH<sub>2</sub>Ph, X = H, R<sub>3</sub> = Me, A = Q) (II). II in vitro inhibited human  $\alpha$ -thrombin with K<sub>i</sub> of  $\leq 1$  nM. A polymorphic **crystalline** form type A and type B monohydrate of II.2HCl were also prepared and claimed. Pharmaceutical compns., e.g. an tablet formulation containing II, were described.

L71 ANSWER 10 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:545815 HCAPLUS  
 DOCUMENT NUMBER: 127:225180  
 TITLE: Two methods for the measurement of the dissociation pressure of a **crystalline** hydrate  
 AUTHOR(S): Crocker, Louis S.; Varsolona, Richard J.; Mccauley, James A.  
 CORPORATE SOURCE: Merck Research Laboratories, Analytical Research Department, Rahway, NJ, 07065, USA  
 SOURCE: Journal of Pharmaceutical and Biomedical Analysis (1997), 15(11), 1661-1665  
 CODEN: JPBADA; ISSN: 0731-7085  
 PUBLISHER: Elsevier  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Two methods for the measurement of the characteristic dissociation pressures of a system containing water vapor and two different **crystalline** hydrates of the pharmaceutical compound MK-0677 are described. One method involves the spectroscopic determination of water in gases equilibrated with the solids at controlled temps., using an IR spectrometer. The second method utilizes the extrapolated onset temperature of the transition from one hydrate to the other at controlled humidities, as observed by differential scanning calorimetry. The methods give similar results for the system of interest.  
 REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L71 ANSWER 11 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:513504 HCAPLUS  
 DOCUMENT NUMBER: 127:149281  
 TITLE: Process for the production of finasteride polymorphic form I via **crystallization**  
 INVENTOR(S): McCauley, James A.; Varsolona, Richard J.  
 PATENT ASSIGNEE(S): Merck and Co., Inc., USA  
 SOURCE: U.S., 6 pp., Cont.-in-part of U.S. 5,468,860.  
 CODEN: USXXAM  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5652365	A	19970729	US 1995-411685	19950330
US 5468860	A	19951121	US 1993-10734	19930129
WO 9411387	A2	19940526	WO 1993-US10659	19931105
WO 9411387	A3	19940929		
W: BB, BG, BR, BY, CZ, FI, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ				
RW: BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
PL 179379	B1	20000831	PL 1993-309050	19931105
US 5886184	A	19990323	US 1997-824426	19970326
PRIORITY APPLN. INFO.:			US 1992-978535	B2 19921119

US 1993-10734 A2 19930129  
 WO 1993-US10659 W 19931105  
 US 1995-411685 A3 19950330

AB Polymorphic form I of finasteride, 17 $\beta$ -(N-tert-Bu carbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one, is produced in substantially pure form using the steps of: (1) **crystallization** from a solution of finasteride in a water immiscible organic solvent and 0% or more by weight of water, producing solvated and non-solvated finasteride in solution, such that the amount of organic solvent and water in the solution is sufficient to cause the solubility of the non-solvated form of finasteride to be exceeded and the non-solvated form of finasteride to be less soluble than any other form of finasteride in the organic solvent and water solution: (2) recovering the resultant solid phase; and (3) removing the solvent therefrom; wherein the water immiscible organic solvent is Et acetate or iso-Pr acetate and the amount of water in the solvent mixture is below 4 mg./mL.

L71 ANSWER 12 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:394288 HCAPLUS

DOCUMENT NUMBER: 127:5081

TITLE: Preparation of polymorphic forms of a growth hormone release stimulant

INVENTOR(S): Draper, Jerome P.; Dubost, David C.; Kaufman, Michael J.; McCauley, James A.; Vandrilla, Jennifer L.; Varsolona, Richard J.

PATENT ASSIGNEE(S): Merck and Co., Inc., USA

SOURCE: PCT Int. Appl., 85 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9715574	A1	19970501	WO 1996-US16955	19961023
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2235371	AA	19970501	CA 1996-2235371	19961023
AU 9674686	A1	19970515	AU 1996-74686	19961023
AU 707946	B2	19990722		
JP 10512295	T2	19981124	JP 1996-516737	19961023
BR 9611229	A	19990525	BR 1996-11229	19961023
EP 1019402	A1	20000719	EP 1996-936869	19961023
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 3204266	B2	20010904	JP 1997-516737	19961023
ZA 9608989	A	19970429	ZA 1996-8989	19961025
NO 9801867	A	19980629	NO 1998-1867	19980424
HK 1017894	A1	20010928	HK 1999-102961	19990712
PRIORITY APPLN. INFO.:			US 1995-5900P	P 19951027
			GB 1996-3361	A 19960216
			WO 1996-US16955	W 19961023

AB The title stimulant (no data), N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate was

prepared in a multistep synthesis and converted to multiple characterized polymorphic forms. The instant polymorphic forms have advantages over the other known forms in terms of thermodyn. stability and suitability for inclusion in pharmaceutical formulations.

L71 ANSWER 13 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:567328 HCAPLUS  
DOCUMENT NUMBER: 125:188360  
TITLE: Thermodynamically stable **crystal** form of  
4"-deoxy-4"-epi-methylamino avermectin bla/blb benzoic  
acid salt and processes for its preparation  
INVENTOR(S): Cvetovich, Raymond; Demchak, Richard; Mccauley, James  
A.; Varsolona, Richard J.  
PATENT ASSIGNEE(S): Merck and Co., Inc., USA  
SOURCE: PCT Int. Appl., 14 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 3  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9622300	A1	19960725	WO 1996-US459	19960116
W:	AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AZ, BY, KG, KZ, RU			
RW:	KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
US 6486195	B1	20021126	US 1995-376318	19950120
AU 9646990	A1	19960807	AU 1996-46990	19960116
PRIORITY APPLN. INFO.:			US 1995-376318	A 19950120
			US 1993-109189	B2 19930819
			WO 1996-US459	W 19960116

AB The most thermodynamically stable **crystalline** form of the benzoic acid salt of 4"-epi-methylamino avermectin Bla/B1b as the hemihydrate is obtained by **crystallization** from organic solvents containing a controlled amount of water. The obtained product is referred to as **crystal** form B or Type B, and is designated for use as an agricultural insecticide.

L71 ANSWER 14 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:1006742 HCAPLUS  
DOCUMENT NUMBER: 124:117692  
TITLE: New finasteride processes  
INVENTOR(S): Dolling, Ulf H.; McCauley, James A.; Varsolona, Richard J.  
PATENT ASSIGNEE(S): Merck and Co., Inc., USA  
SOURCE: U.S., 4 pp. Cont.-in-part of U.S. Ser. No. 978,535, abandoned.  
CODEN: USXXAM  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 3  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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US 5468860	A	19951121	US 1993-10734	19930129
WO 9411387	A2	19940526	WO 1993-US10659	19931105
WO 9411387	A3	19940929		
W: BB, BG, BR, BY, CZ, FI, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ				
RW: BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
RU 2120445	C1	19981020	RU 1995-112521	19931105
RO 115164	B1	19991130	RO 1995-940	19931105
RO 115165	B1	19991130	RO 1999-785	19931105
CZ 287842	B6	20010214	CZ 1995-1268	19931105
SK 281765	B6	20010710	SK 1995-659	19931105
PL 186740	B1	20040227	PL 1993-333738	19931105
IL 107574	A1	20000716	IL 1993-107574	19931111
IL 125769	A1	20030312	IL 1993-125769	19931111
IL 125770	A1	20040219	IL 1993-125770	19931111
EP 599376	A2	19940601	EP 1993-203163	19931112
EP 599376	A3	19940928		
EP 599376	B1	19980408		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
EP 655458	A2	19950531	EP 1995-200270	19931112
EP 655458	A3	19960710		
EP 655458	B1	19990303		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
EP 823436	A2	19980211	EP 1997-201712	19931112
EP 823436	A3	19981125		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
AT 164850	E	19980415	AT 1993-203163	19931112
ES 2052476	T3	19980616	ES 1993-203163	19931112
AT 177112	E	19990315	AT 1995-200270	19931112
ES 2072848	T3	19990501	ES 1995-200270	19931112
CA 2103107	AA	19940520	CA 1993-2103107	19931115
AU 9350787	A1	19940616	AU 1993-50787	19931118
AU 658774	B2	19950427		
JP 06199889	A2	19940719	JP 1993-289536	19931118
JP 07110875	B4	19951129		
ZA 9308620	A	19940804	ZA 1993-8620	19931118
HU 66973	A2	19950130	HU 1993-3275	19931118
HU 216195	B	19990528		
JP 09235294	A2	19970909	JP 1996-259373	19931118
HR 931410	B1	20000630	HR 1993-931410	19931118
CN 1090583	A	19940810	CN 1993-114530	19931119
CN 1058018	B	20001101		
US 5652365	A	19970729	US 1995-411685	19950330
FI 9502422	A	19950518	FI 1995-2422	19950518
NO 9501986	A	19950519	NO 1995-1986	19950519
US 5886184	A	19990323	US 1997-824426	19970326
HK 1008338	A1	20000505	HK 1998-109309	19980721
LV 12212	B	19990320	LV 1998-236	19981026
NO 9900468	A	19950519	NO 1999-468	19990201
NO 9902580	A	19950519	NO 1999-2580	19990528
LV 12460	B	20000920	LV 2000-26	20000223
HR 2000000295	A1	20000831	HR 2000-295	20000512
HR 20000295	B1	20020831		
FI 2001000289	A	20010215	FI 2001-289	20010215
FI 2001000290	A	20010215	FI 2001-290	20010215
FI 2004000559	A	20040421	FI 2004-559	20040421
PRIORITY APPLN. INFO.:				
			US 1992-978535	B2 19921119
			US 1993-10734	A 19930129
			WO 1993-US10659	W 19931105
			IL 1993-107574	A3 19931111

EP 1993-203163 A3 19931112  
 JP 1993-289536 A3 19931118  
 US 1995-411685 A3 19950330

OTHER SOURCE(S): CASREACT 124:117692

AB Finasteride is prepared by treating a carboxylic ester analog with Me<sub>3</sub>CNH<sub>2</sub> in presence of an organomagnesium halide, present in at least a 2:1 molar ratio to the ester. Two polymorphic **crystalline** forms of finasteride are also prepared. Thus, Me 3-oxo-4-aza-5 $\alpha$ -andro-1-en-17 $\alpha$ -carboxylate was treated with Me<sub>3</sub>CNH<sub>2</sub> and 2 mol of EtMgBr to give 97% finasteride.

L71 ANSWER 15 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:994313 HCAPLUS

DOCUMENT NUMBER: 124:86818

TITLE: Preparation and characterization of the different **crystal** forms of (+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl)-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidinyl]yl]methanesulfonamide hydrochloride

INVENTOR(S): Desmond, Richard; Tschaen, David M.; McCauley, James A.; Varsolona, Richard J.

PATENT ASSIGNEE(S): Merck and Co., Inc., USA

SOURCE: PCT Int. Appl., 28 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

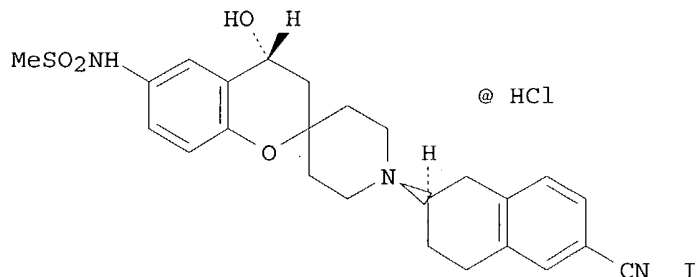
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9523146	A1	19950831	WO 1995-US2265	19950223
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9518820	A1	19950911	AU 1995-18820	19950223
PRIORITY APPLN. INFO.:			US 1994-201841	19940225
			WO 1995-US2265	19950223

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AB The 9 different morphol. forms of the antiarhythmic (+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl)-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidinyl]yl]methanesulfonamide hydrochloride (I) are

prepared by selective **crystallization** or precipitation and characterized.

L71 ANSWER 16 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:994187 HCAPLUS

DOCUMENT NUMBER: 124:55978

TITLE: Process for making HIV protease inhibitors containing  
N-tert-butyl-2-piperazinecarboxamide derivative

INVENTOR(S): Rossen, Kai; Askin, David; Reider, Paul;  
**Varsolona, Richard J.**; Volante, Ralph

PATENT ASSIGNEE(S): Merck and Co., Inc., USA

SOURCE: PCT Int. Appl., 57 pp.

CODEN: PIXXD2

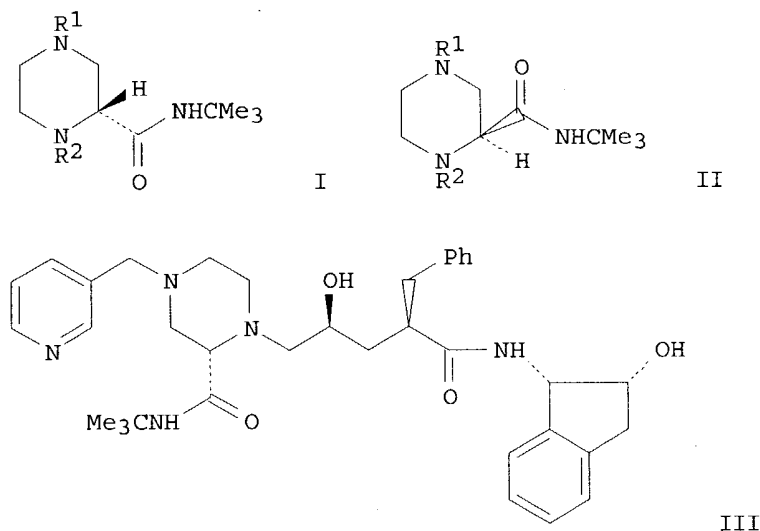
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9521162	A1	19950810	WO 1995-US1232	19950130
W:	AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, UZ			
RW:	KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
TW 472047	B	20020111	TW 1995-84100727	19950127
CA 2180947	AA	19950810	CA 1995-2180947	19950130
AU 9516967	A1	19950821	AU 1995-16967	19950130
AU 691878	B2	19980528		
EP 741712	A1	19961113	EP 1995-908747	19950130
EP 741712	B1	20011004		
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE			
HU 76303	A2	19970728	HU 1996-2143	19950130
JP 09508628	T2	19970902	JP 1995-520686	19950130
BR 9506727	A	19970923	BR 1995-6727	19950130
RU 2135482	C1	19990827	RU 1996-117468	19950130
SK 281861	B6	20010806	SK 1996-1006	19950130
AT 206407	E	20011015	AT 1995-908747	19950130
ES 2161863	T3	20011216	ES 1995-908747	19950130
RO 118292	B1	20030430	RO 1996-1576	19950130
CZ 291774	B6	20030514	CZ 1996-2272	19950130
US 5663341	A	19970902	US 1995-487903	19950607
FI 9603054	A	19960801	FI 1996-3054	19960801
PRIORITY APPLN. INFO.:			US 1994-192916	A 19940204
			WO 1995-US1232	W 19950130
OTHER SOURCE(S):	MARPAT 124:55978			
GI				



AB A process for racemization of optically pure or enriched piperazine-2-tert-butylcarboxamide and its derivs. (I or II; R1, R2 = H R, COR, CO2R; wherein R = C1-5 alkyl, arylmethyl, heteroarylmethyl, aryl, CF3) comprises reacting the optically pure or enriched piperazine compound with a racemizing agent selected from a strong base, an anhydrous metal salt or a carboxylic acid, in a solvent at a temperature range of between room temperature

and 250°. The piperazine carboxamide derivs. are key intermediates in the preparation of HIV protease inhibitor compds., including Compound J (III).

Thus, 0.21 mol L-pyroglutamic acid and 5 mL H2O were added to a solution of 0.11 mol (RS)-2-(tert-butylcarboxamido)piperazine in 155 mL n-propanol and the resulting slurry was heated to reflux to give a homogeneous yellow solution which was cooled to 50°, seeded with (R)-2-(tert-butylcarboxamido)piperazine.L-pyroglutamic acid salt (IV), cooled to 25°, aged for 16 h, and filtered to give, after washing with 35 mL cold n-propanol/1% H2O, 48% IV of 98% e.e. The yellow mother liquor containing 46% (S)-2-(tert-butylcarboxamido)piperazine.L-pyroglutamic acid salt were evaporated to give the salt which (50.1 mmol) was dissolved in 226 mL n-propanol and 35.5 mL Et3N and treated with a solution of 50.1 mmol Boc2O in 24 mL EtOAc over 2 h to give, after workup and **crystallization**, S-isomer II (R1 = Boc, R2 = H) (V) of >99.9% e.e. The R-isomer salt IV (0.468 mol) was treated with a mixture of 80 mL 50% NaOH, 700 mL H2O, and 40 mL n-propanol to give R-isomer I (R1 = R2 = H) (VII), which was heated and racemized with Me3COK in a mixture of cyclohexane and THF to reflux for 7 h, cooled to 2° for 2 h, and filtered to give, after washing with cyclohexane and drying, a white **crystalline** powder containing 50.8% R-isomer VII and 49.2% S-isomer II (R1 = R2 = H) (VIII). This racemate can be similarly resolved to give the desired S-isomer VIII. The S-isomer V was converted into Compound J III in 4 steps.

L71 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:557962 HCAPLUS

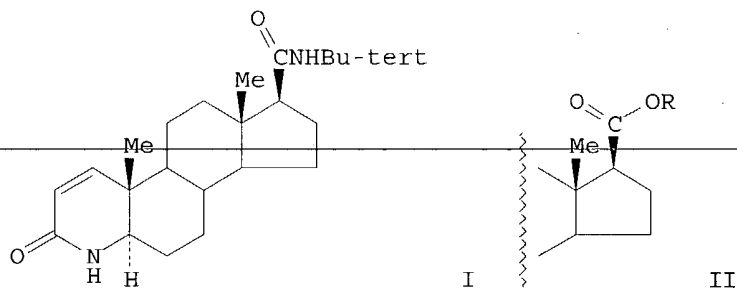
DOCUMENT NUMBER: 121:157962

TITLE: A process for the production of finasteride and its polymorphs

INVENTOR(S): Dolling, Ulf H.; McCauley, James A.; Varsolona,

**Richard J.**  
 PATENT ASSIGNEE(S): Merck and Co., Inc., USA  
 SOURCE: Eur. Pat. Appl., 11 pp.  
 CODEN: EPXXDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 599376	A2	19940601	EP 1993-203163	19931112
EP 599376	A3	19940928		
EP 599376	B1	19980408		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5468860	A	19951121	US 1993-10734	19930129
EP 655458	A2	19950531	EP 1995-200270	19931112
EP 655458	A3	19960710		
EP 655458	B1	19990303		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
EP 823436	A2	19980211	EP 1997-201712	19931112
EP 823436	A3	19981125		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
PRIORITY APPLN. INFO.:		US 1992-978535	A	19921119
		US 1993-10734	A	19930129
		EP 1993-203163	A3	19931112
OTHER SOURCE(S):		CASREACT 121:157962; MARPAT 121:157962		
GI				



AB The 5α-reductase inhibitor finasteride (I) is prepared by reaction of 17β-carboalkoxy-4-aza-5α-androst-1-en-3-ones II [R = C1-10 linear, branched, or cyclic alkyl with optional Ph substituent(s)], as their Mg halide salts, with t-butylaminomagnesium halide, present in at least a 2:1 molar ratio to II, formed from tert-BuNH<sub>2</sub> and an aliphatic/aryl magnesium halide at ambient temperature in an inert organic solvent under an inert

atmospheric, followed by heating and recovering I. In 2 examples using II (R = Me), EtMgBr, and tert-BuNH<sub>2</sub>, under N in refluxing THF (12 h), I was prepared in 97% yield. Also disclosed are 2 polymorphic **crystalline** forms of I, and methods of their production. Dissolving I in glacial AcOH and adding H<sub>2</sub>O up to ≥84 weight% H<sub>2</sub>O gives form I, whereas adding H<sub>2</sub>O up to 75-80 weight% H<sub>2</sub>O gives form II.

L71 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 1993:633857 HCAPLUS  
 DOCUMENT NUMBER: 119:233857

TITLE: The effect of polymorphism and metastability on the characterization and isolation of two pharmaceutical compounds

AUTHOR(S): McCauley, J. A.; Varsolona, R. J.; Levorse, D. A.

CORPORATE SOURCE: Merck Res. Lab., Rahway, NJ, 07065, USA

SOURCE: Journal of Physics D: Applied Physics (1993), 26(8B), B85-B89  
CODEN: JPAPBE; ISSN: 0022-3727

DOCUMENT TYPE: Journal

LANGUAGE: English

AB L-706,000, a class III antiarrhythmic compound, exists in several different **crystalline** structures including two anhydrous polymorphs, two dihydrated enantiotropic polymorphs, a monohydrate and several organic solvent solvates. The isolation of the desired **crystal** modification, dihydrate type A, can be accomplished under thermodyn. or kinetic control depending on the conditions. Under kinetic control, the isolation depends on a suspended transformation of a metastable state. L-700,462, a thrombotic agent, exists in three **crystalline** structures: a monohydrate and two anhydrous monotropic polymorphs. Both anhydrous polymorphs, when hydrated, yielded the single monohydrate. Drying of the monohydrate, depending on the conditions and sample, will give either anhydrous form. The varying results obtained upon drying are, once again, indicative of the presence of metastable states and suspended transformations in connection with the solid state of L-700,462.

L71 ANSWER 19 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1990:534506 HCAPLUS

DOCUMENT NUMBER: 113:134506

TITLE: Contact nuclei formation in aqueous dextrose solutions

AUTHOR(S): Cerreta, Michael K.; Berglund, Kris A.

CORPORATE SOURCE: Dep. Chem. Eng., Michigan State Univ., East Lansing, MI, 48824, USA

SOURCE: Journal of Crystal Growth (1990), 102(4), 869-76  
CODEN: JCRGAE; ISSN: 0022-0248

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A laser Raman microprobe was used in situ to observe the growth of alpha dextrose monohydrate on alpha anhydrous dextrose **crystals**. The Raman spectra indicated growth of the monohydrate below 28.1°, but the presence of only the anhydrous form above 40.5°. Contact nucleation expts. with parent anhydrous **crystals** yielded only monohydrate nuclei below 28.1°, whereas contacts in solns. between 34.5 and 41.0° produced both **crystalline** forms, and contacts in solns. above 43.5° produced only anhydrous nuclei. The inability of the monohydrate to grow on anhydrous **crystals** in the same solution that formed the two **crystalline** phases with a single contact precluded a simple attrition mechanism of nuclei formation. For the same reason, the hypothetical mechanism involving parent **crystal** stabilization of pre-**crystalline** of pre-**crystalline** clusters, allowing the clusters to grow into nuclei, was also contradicted. A third, mechanism, which might be a combination of the two, was believed to apply.

L71 ANSWER 20 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1988:83139 HCAPLUS

DOCUMENT NUMBER: 108:83139

TITLE: The structural effects of pH on concentrated aqueous ammonium dihydrogen phosphate by laser Raman spectroscopy

AUTHOR(S): **Cerreta, Michael K.; Berglund, Kris A.**  
CORPORATE SOURCE: Dep. Chem. Eng., Michigan State Univ., East Lansing,  
MI, 48824, USA  
SOURCE: Cryst. Precip., Proc. Int. Symp. (1987), 53-9.  
Editor(s): Strathdee, Graeme L.; Klein, M. O.; Melis,  
L. A. Pergamon: Oxford, UK.  
CODEN: 56FAAU  
DOCUMENT TYPE: Conference  
LANGUAGE: English

AB The structure of pure, concentrated aqueous solns. of dihydrogen orthophosphates is composed of "free" and H-bonded anions. The influence of pH on the structure of ammonium dihydrogen phosphate solns. from pH 3.8 to 5.0 was investigated by laser Raman spectroscopy. Except for the appearance of the (OH)P-O3 sym. stretching vibration, the spectra show little evidence of structural breakup that could account for the increased ease of **crystal** growth at the higher pH.

L71 ANSWER 21 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1988:12218 HCAPLUS

DOCUMENT NUMBER: 108:12218

TITLE: The structure of aqueous solutions of some dihydrogen orthophosphates by laser Raman spectroscopy

AUTHOR(S): **Cerreta, Michael K.; Berglund, Kris A.**

CORPORATE SOURCE: Dep. Chem. Eng., Michigan State Univ., East Lansing,  
MI, 48824, USA

SOURCE: Journal of Crystal Growth (1987), 84(4), 577-88  
CODEN: JCRGAE; ISSN: 0022-0248

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Laser Raman studies at 700-1350 cm<sup>-1</sup> for powdered **crystals** and 0.01 M to saturated aqueous MH<sub>2</sub>PO<sub>4</sub> (M = NH<sub>4</sub>, Na, K) showed that the 875 cm<sup>-1</sup> P(OH)<sub>2</sub> sym. stretch band intensity increased as solute concentration increased and that

an extreme asym. developed toward lower energy in the 1075 cm<sup>-1</sup> P:O<sub>2</sub> sym. stretch band, while the integrated intensity ratio (875/1075 cm<sup>-1</sup> band) remained constant. These results indicate anion-anion H bonding. Deconvolution of spectral bands showed that only 40 and 20% of the H<sub>2</sub>PO<sub>4</sub> exists as monomers in KH<sub>2</sub>PO<sub>4</sub> or (NH<sub>4</sub>)H<sub>2</sub>PO<sub>4</sub> solns., resp., and that anion association does not cease at the dimer stage. There was no evidence for quasi-**crystalline** species in solution. Rapid z-direction growth, growth activation energy, and the rate-limiting surface growth mechanism can be explained in terms of breaking and reforming of H bonds during the growth process.

L71 ANSWER 22 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1985:53233 HCAPLUS

DOCUMENT NUMBER: 102:53233

TITLE: Raman spectroscopic studies of the structure of supersaturated ammonium dihydrogen phosphate solutions

AUTHOR(S): **Cerreta, M. K.; Berglund, K. A.**

CORPORATE SOURCE: Dep. Chem. Eng., Iowa State Univ., Ames, IA, USA

SOURCE: Process Technology Proceedings (1984), 2(Ind. Cryst.),  
233-6  
CODEN: PTPREM; ISSN: 0921-8610

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Raman spectroscopic studies of quiescent undersatd. and supersatd. NH<sub>4</sub>H<sub>2</sub>PO<sub>4</sub> aqueous solns. were performed on the v<sub>1</sub> (totally sym. or breathing mode) and v<sub>3</sub> (sym. twist) H<sub>2</sub>PO<sub>4</sub> bands as well as for the v<sub>1</sub> band of

solid  $\text{NH}_4\text{H}_2\text{PO}_4$  and solid  $(\text{NH}_4)_2\text{HPO}_4$ . The splitting of the nondegenerate  $\text{NH}_4\text{H}_2\text{PO}_4$   $\nu_1$  band in concentrated solution is interpreted in terms of a well-ordered **quasicryst.** solution structure. Increases in  $\nu_1$  half-width at half-height support this view. Changes in the  $\nu_3$  band suggest future avenues of investigation.

L71 ANSWER 23 OF 25 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1997:324157 BIOSIS  
 DOCUMENT NUMBER: PREV199799623360  
 TITLE: The polarizing microscope in pharmaceuticals.  
 AUTHOR(S): Smoliga, John A.  
 CORPORATE SOURCE: Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA  
 SOURCE: Scanning, (1997) Vol. 19, No. 3, pp. 194.  
 Meeting Info.: Proceedings of SCANNING 97. Monterey, California, USA. April 20, 1997.  
 CODEN: SCNNDF. ISSN: 0161-0457.  
 DOCUMENT TYPE: Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 5 Aug 1997  
 Last Updated on STN: 5 Aug 1997

L71 ANSWER 24 OF 25 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1994-0139321 PASCAL  
 COPYRIGHT NOTICE: Copyright .COPYRG. 1994 INIST-CNRS. All rights reserved.  
 TITLE (IN ENGLISH): The effect of polymorphism and metastability on the characterization and isolation of two pharmaceutical compounds  
**Crystal growth of organic materials**  
 AUTHOR: MCCAULEY J. A.; VARSOLONA R. J.; LEVORSE D. A.  
 PUGH David (ed.); ROBERTS Kevin (ed.); SHERWOOD John N. (ed.)  
 CORPORATE SOURCE: Merck Research Laboratories, Rahway NJ 07065, United States  
 Univ. Strathclyde, Glasgow, United Kingdom  
 SOURCE: Journal of physics. D. Applied physics, (1993), 26(8B), B85-B89, 8 refs.  
 Conference: 2 CGOM-2. International workshop, Glasgow (United Kingdom), 7 Sep 1992  
 ISSN: 0022-3727 CODEN: JPAPBE  
 DOCUMENT TYPE: Journal; Conference  
 BIBLIOGRAPHIC LEVEL: Analytic  
 COUNTRY: United Kingdom  
 LANGUAGE: English  
 AVAILABILITY: INIST-5841, 354000035404090120  
 AN 1994-0139321 PASCAL  
 CP Copyright .COPYRG. 1994 INIST-CNRS. All rights reserved.  
 AB L-706,000, a class III antiarrhythmic compound, has been found to exist in several different **crystalline** structures including two anhydrous polymorphs, two dihydrated enantiotropic polymorphs, a monohydrate and several organic solvent solvates. The isolation of the desired **crystal** modification, dihydrate type A, can be accomplished under thermodynamic or kinetic control depending on the conditions. Under kinetic control, the isolation depends on a suspended transformation of a metastable state. L-700,462, a thrombotic agent, has

been found to exist in three **crystalline** structures: a monohydrate and two anhydrous monotropic polymorphs

L71 ANSWER 25 OF 25 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
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ACCESSION NUMBER: 2002383086 EMBASE  
TITLE: Erratum: A spectroscopic and **crystallographic**  
study of polymorphism in an aza-steroid (Journal of  
Pharmaceutical Sciences (2000) 89:10 (1271-1285)).  
AUTHOR: Wenslow R.M.; Baum M.W.; Ball R.G.; McCauley J.A.;  
**Varsolona R.J.**  
CORPORATE SOURCE: R.M. Wenslow, Merck Research Laboratories, 126 E. Lincoln  
Avenue, Rahway, NJ 07065-0900, United States  
SOURCE: Journal of Pharmaceutical Sciences, (1 Nov 2002) 91/11  
(2465).  
ISSN: 0022-3549 CODEN: JPMSAE  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Errata  
FILE SEGMENT: 039 Pharmacy  
LANGUAGE: English

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